ALIMENTARY ANAPHYLAXIS

LAROCHE—RICHET—SAINT GIRONS

ROWE

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ALIMENTARY ANAPHYLAXIS

(Gastro-intestinal Food Allergy)

BY

GUY LAROCHE, CHARLES RICHET FILS

AND

FRANÇOIS SAINT-GIRONS

PARIS, FRANCE

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PREFACE

Food allergy as a cause of gastro-intestinal symptoms has been recognized in childhood by American, English, and French physicians for many years and the importance of food allergy in the production of various syndromes in adult life is becoming more apparent to students of this subject. So many interesting phases of this problem of food sensitization are presented in this monograph by Laroche, Richet, and Saint-Girons that I believe many physicians will profit by the study of their record, especially because of the scarcity of contributions which have been published in English on gastro-intestinal allergy.

Though this monograph is particularly interesting from the historical viewpoint as the first extended contribution and summary of gastro-intestinal allergy, it contains much information which is not appreciated today by the average physician. The frequency of food allergy is becoming more and more evi-

dent and it is my conviction that it plays a frequent rôle in the production of many marked as well as mild symptoms. As Richet says, "Allergy is active every day in modifying our perpetually unstable state of equilibrium and in establishing for us a humoral personality." This makes it imperative for physicians, including the various specialists, to become acquainted with such manifestations in order to recognize this etiological factor in their patients. This monograph, moreover, reviews many experimental studies and makes certain suggestions of theoretical and therapeutic value which are stimulating to thought as well as useful for present-day practice. Though it is true that certain experimental evidence and clinical experience now apparently disprove some of the opinions of the writers as published a decade ago, there remains a large amount of important information in the monograph. Of special value are the notes written by the authors within the last few months, which are printed as footnotes.

In the following pages I will discuss the monograph and these recently written "notes" from my personal reaction and in light of the attitude held by certain students of food allergy here in America. The authors have used "anaphylaxis" for "allergy" as it is used in this country, and in translating the original text, we have chosen to retain the former term.

The writers call attention to the variety of symptoms, such as sick headache, abdominal pain, vomiting, diarrhea, and chronic colitis that may result from food allergy. It is interesting that they term the vomiting resulting from food sensitization "the protective vomiting of anaphylaxis."

My experience as well as that of Duke, Vaughan, Alexander, Eyermann, Cooke, Balyeat, and others in America indicates that food allergy may be one of the causes of urticaria, eczema, angioneurotic edema, migraine, convulsions, perennial hay fever, chronic bronchitis, bronchial asthma, various gastrointestinal symptoms, and certain other condi-

tions. This large number of manifestations was not entirely recognized by the authors in their monograph, because of the early period of their studies, though they suggested that many of them would eventually be shown to be due to food sensitization. In a recent article, I reported a series of one hundred gastro-intestinal cases in which food allergy was productive of canker sores, heavy breath, gastric distress, belching, localized or diffuse abdominal pain (simulating at times that due to ulcer, gall bladder, appendix, or intestinal obstruction), diarrhea, constipation, chronic colitis, or pruritus ani. This emphasizes the importance of the consideration of this type of sensitization in all gastro-intestinal investigations.

The authors describe a state of chronic anaphylaxis which they state is now of "classical importance," which has been described by me under the term "allergic toxaëmia" characterized by fatigue, aching, mental confusion, irritability, and restlessness. In my opinion this chronic allergic state is not

uncommon, and is often associated with migraine, gastro-intestinal allergy, or other symptoms due to food sensitization. The authors also emphasize the occurrence of both mild and severe allergic symptoms indicated by them under the classification of "Little A" and "Great A." This recognition of all types of symptoms including the mild ones which are difficult to diagnose, the moderately severe, and the markedly severe ones is most important for the accurate investigation of patients.

The discussion of milk allergy by the writers of this monograph is of great interest and importance to all physicians, especially to those dealing with infants and children. Milk sensitization is now being recognized as a common cause of colic, abdominal pain, and flatulence in infants, and at times, as mentioned by the authors, of cyclic vomiting and of convulsions. Many of the feeding problems of childhood can be explained by food allergy. The presence of a group allergy to the milks of various animals is noted and is

now known to be due to the identity of the caseins of various types of milk, sensitization to the lact-albumens however being specific for each milk. The fact that the milk of a mother or a wet nurse may disagree with an infant when that of another nurse will not is explained today by the presence of a food protein in the milk to which the child is sensitive and may be remedied by the exclusion of the specific food from the mother's or nurse's diet. The cases of Finizio as reported by the writers are of special interest because of the development of symptoms after the first administration of milk, indicating an inherited allergy or a sensitization *in utero* or during nursing produced by the cow's milk protein present in the mother's blood or in her milk. Hutinel's description of the manifestations of milk allergy is dramatic and remarkable, and the report of three deaths resulting from milk sensitization and preceded by vomiting, bloody diarrhea, dyspnoea, cyanosis, and convulsions emphasizes the importance of the study of food allergy

by all physicians. The possibility of sensitization to milk protein by the temporary administration of cow's milk until the breast milk appears, makes such feeding of questionable value. Chronic milk allergy is recognized by the writers as producing emaciation and progressive loss of weight, indigestion, and often vomiting or diarrhea and is at times associated with eczema, prostration, weakness, and temperature varying from 34.4 degrees to 40 degrees C.

The presentation of egg sensitization is of interest and help to the reader. The case of Gelpke, in which egg allergy produced urticaria, diarrhea, and severe abdominal pain identical with the symptoms occurring in the mother indicates the inheritance of specific food manifestations, which in my experience occasionally occurs. The minute amount of egg which produced violent symptoms in the case of Landmann as well as of Horwitz emphasizes the importance of the exclusion of the minutest particle of a food such as egg to which a patient is sensitive.

The case of Brazis in which egg produced immediate suffocation, vomiting, abdominal pain, and a burning throughout the entire skin of the body, with tingling in the throat and ears, and the appearance of an immediate hive in the skin where the patient had accidently pricked herself with a pin with which she had opened an egg is illustrative of the marked type of sensitization produced by this food.

The varying time of appearance of symptoms in food-sensitive patients is indicated by the case reports. The writers mention periods varying from a few seconds to 45 minutes. I have records of longer delays in onset of the allergic reactions. In one instance of garlic susceptibility, the delay varied from 16 to 18 hours, and many cases with the appearance of symptoms in 4–12 hours have been studied. Such variation is possibly due to the different location of the permeable or sensitized mucosa in the gastro-intestinal tract.

The comment by the writers on the allergic reactions which may result from shell fish, especially oysters, mussels, as well as gudgeon, emphasizes a type of food allergy which may be violent and which is easily recognized by the patient. The fact that sensitization may occur to all types of food, especially to the most common ones such as wheat, milk, and eggs was not realized at the time of the publication of the original monograph. The authors recently mention such sensitizations commenting on their failure to appreciate the frequency of wheat allergy, especially in adult life.

In their discussion of the pathogenesis of food allergy, increased permeability of mucous membrane with a possible liver insufficiency which fails to prevent the food proteins from entering the blood stream is offered as a possible explanation. Today this remains as the most likely cause but the reason for increased membrane permeability and the method of its prevention are unsolved problems of great importance in food allergy.

Enteritis in infants and intestinal disturbances in adults are recognized as possible predisposing factors for the entrance of foreign proteins into the blood stream. The writers also realize that the intestinal mucosa of newborn infants is especially liable to increased permeability. Of marked interest is the comment on Claude Bernard's old experiment demonstrating the ability of the liver to remove protein from the blood. Experimental production of liver lesions in sensitized animals, and the finding of pathological changes in the livers of sensitized infants by Barbier and Clariet substantiate the probability that the liver is the seat of allergic reactions in human beings, giving rise to discomfort and possible physiological disturbances in the liver itself. The writers suggest that a disturbance in the vagosympathetic equilibrium and possibly in the internal secretions may be at the basis of the tendency to food sensitization and their comments on these possibilities are of marked interest. It is suggested that gastric symptoms such

as those reported in one patient from a single drop of vinegar may be due to a lesion comparable to those occurring in the Arthus phenomenon. This chapter on pathogenesis is stimulating to thought and though much investigation has already been carried out on the various problems, the suggested fields of possible experimentation are extensive.

Insufficiency of gastric and pancreatic ferments as a possible cause of food allergy is discussed and favored by the authors. An inherited deficiency of digestive juices may be responsible for food sensitization in some infants, especially in view of the delayed appearance of such juices in most babies. It is interesting, moreover, that Dreyfus and others, as reported by the writers of the monograph, found that sensitization is produced better experimentally by rectal injection than by ingestion. Clinical experience has now made it evident that food sensitization does not depend on the absence of digestive ferments in the usual case even though such deficiency at times may be in-

strumental in the establishment of food allergy in infants. Moreover, the endeavor to prevent food allergy by digesting food proteins into inactive products with ferments administered by mouth is thereotically difficult to accept in practice and has given indifferent results in my experience.

The experimental studies bearing on the problem of food allergy discussed by the writers are of definite interest and stimulation today and may be read with profit by all physicians studying this problem. The successful production of food sensitization in animals by ingestion as reported by Richet is described. Of special interest and possible clinical value is his finding that large feedings over a limited period of time are more likely to produce sensitization than are small ones and that continued ingestions over a period of weeks fail to result in sensitization. Experimentally it was found that the boiling of milk does not destroy its sensitizing proteins. In view of recent clinical reports on the successful use of milk which has been

boiled for 4–6 hours, or heated to temperatures of 260° F., similar experiments with such milk should be repeated. Kleinschmidt's and especially Richet's experimental studies on alimentary allergy to milk and eggs are of interest and importance. The former was unable to desensitize animals by previous ingestion of the food to which allergy had been established.

The discussion of the cause or mechanism of anaphylaxis is well presented. The chemical, biological, and physical theories of anaphylaxis are outlined. The authors are unable to decide which one is correct and in their recent notes feel that a probable combination of all the theories may be the correct explanation. Richet agrees with Wells and Osborne that anaphylaxis may be the first stage of immunity, that both are definitely related, and that anti-anaphylaxis and immunity are possibly identical.

In diagnosis, recognition of the mild or chronic food allergies is most important from the clinical viewpoint and must necessarily

be appreciated by the American and English physicians. The slow reappearance of symptoms on the retaking of food after a period of abstinence is important to remember. Under laboratory diagnosis, passive anaphylaxis and precipitin reactions are discussed. Further investigation along these lines especially on chronic food allergy needs to be done to aid in the laboratory diagnosis of this condition.

No discussion of skin reactions, which is essentially an American contribution, is made by the authors. I feel that positive skin reactions when checked by food trial are of unquestioned value and that the history of food dislikes and disagreements and of an allergic status in the patient or his family is of definite aid in pointing toward the possibility of food allergy in the patient. My emphasis of the frequency of negative skin reactions to foods, the necessity of diet trial even in the presence of skin reactions, and the importance of determining food allergy by diet trial, especially by elimination

diets such as I have proposed, is of great importance if all the manifestations of food allergy in patients seen by the physician today are recognized.

The section on treatment contains many helpful suggestions. Prevention of food sensitization is of great importance, though probably difficult to carry out in susceptible patients. Overfeeding, especially in infants or children or after illness in adult life, is pointed out as unwise. In cow's milk allergy the use of nurse's milk or that of the ass or goat or a carbohydrate diet is suggested. Danger of resumption of cow's milk is stressed. Schlossmann suggests the immunization to cow's milk by the injection of gradually increasing doses of beef serum. The desensitization of the milk-sensitive child with gradually increasing amounts of a pap made by the long boiling of milk with cereal is recommended and has been used in certain American clinics. The use of ether or camphorated oil in the treatment of acute reactions has not found favor in this country.

Finally the author's recommendations of auto-hemotherapy are of interest and the use of a small meal one hour before eating may be of help. Peptone has not been so successfully used here in America as has been reported by the French and English physicians. My own experience indicates the value of the exclusion of foods causing allergic symptoms as determined by food tests and by my elimination diets. Desensitization occurs frequently with such elimination over a period of weeks. The use of heated foods as melba toast or boiled or dried milk as well as oral desensitization to the important foods has been of some help in my work.

As previously stated, this monograph is of definite historical interest and value but, as I have tried to emphasize, it contains much information and many stimulating suggestions, and outlines a broad field of experimental investigation which is as applicable today to the problem of food allergy as it was a decade ago. To students of allergy I feel that an available translation, with its bibli-

ography, will be of definite service in the study of gastro-intestinal allergy and in indicating the field of accomplishment by our professional confrères in France.

ALBERT H. ROWE.

OAKLAND, CALIFORNIA
October 4, 1929

ALIMENTARY ANAPHYLAXIS

Gastro-intestinal Food Allergy

FOREWORD

It is obvious that the study of alimentary anaphylaxis has inspired the young physicians who have written this instructive little book for they have been able to compile a treatise of experimental and clinical observations in a scholarly manner.

Of the many chapters on anaphylaxis, that on alimentary anaphylaxis is the one which deals most with medical practice, for it gives an acceptable physiological and scientific explanation to that which older doctors have called "idiosyncrasy." We know now that, in at least a large number of cases whose history can be accurately studied, this curious idiosyncrasy in digestion which excited the astonishment of our fathers, is explained by anaphylaxis. In fact,

it is relatively rare, in human beings, that heterogeneous substances penetrate into the tissues in any way other than through the digestive tract. Subcutaneous injections of albuminoid products are, on the whole, exceptional occurrences. But, aside from the stings of poisonous insects and the therapeutic injections of serum, the proteins never penetrate into the circulation without having been submitted to the action of the digestive juices.

As nature protects its children admirably, the proteins introduced into the digestive tube undergo profound chemical changes which make them harmless. So alimentary anaphylaxis, that is to say, the penetration of unchanged proteins, is the exception. We ingest a quantity of albumens, but these albumens do not anaphylactize.

Why do we become anaphylactic? Four hypotheses are available (among which it is very difficult to choose) for the explanation of the special cases of alimentary anaphylaxis that have been reported.

1. The absorption of food occurs so quickly that the proteins pass into the circulation without having had time to be changed. The epithelial barrier which is opposed to absorption is powerless, whether it be because there is an erosion of the mucous membrane, or because the mass of absorbable protein introduced is so large that some particles pass through the membranes before their transformation.

2. The digestive juices are changed, and consequently powerless to transform the proteins. There may be an impaired digestion (gastric or intestinal) and because of the continued presence of undigested food in the digestive tract abnormal absorption results.

3. In certain persons, as a consequence of a special and unusual action of the digestive juices, there are produced certain substances which are not produced in normal people, and which consequently can successively initiate and precipitate the anaphylactic condition.

4. Finally, there may be in the blood of certain individuals special substances not existing in normal individuals, and these special substances represent a toxogenin of at least one of those substances which, in combination with the antigen, precipitates the anaphylactic condition, just as has been so definitely shown in experimental anaphylaxis.

Summing it up, and in a schematic form, we may believe, from all the special cases which can be cited, that we can have anaphylaxis:

First, by an abnormality of too rapid absorption.

Second, by an abnormality of inefficient digestive juices.

Third, by an abnormality of digestive juices producing special fermentations.

Fourth, by an abnormality of the blood, containing some toxogenic substances.

It is evident that under normal conditions we are protected against the penetration of certain proteins by a sort of immunity, so much so that we can consider the addition of

another abnormality, probably more frequent than the others, to these four fundamental causes; namely, the condition of non-immunity in the blood. According to all evidence, there pass into the blood appreciable quantities of non-transformed proteins; but we are usually well immunized against these proteins, to such a degree that the cases of anaphylaxis that are observed are due rather to an absence of immunity than to a true anaphylaxis.

After having read this little book, the medical men will be able to decide among the different hypotheses which are presented. But for my part, I am led to believe that there is no identity among the different alimentary anaphylaxes, and that each clinical case must be studied alone if one is to obtain a comprehensive idea of this difficult problem.

CHARLES RICHET.

CHAPTER I

INTRODUCTION AND ETIOLOGY[1]

I. Introduction

In 1902 Charles Richet created the term anaphylaxis in order to designate "the curious tendency that certain poisons possess of increasing instead of diminishing the sensitivity of the organism to their action." Certain authors, in particular P. Courmont, observed certain phenomena which did not occur in normal subjects, but it is from the experiments of Richet and Portier that a definite knowledge of the principles of this subject arose. These authors stated, in fact, that some dogs injected for the first time with a non-fatal dose of actinocongestin re-

[1] The authors have just reread this monograph and have had the satisfaction of verifying the ideas on food anaphylaxis which were formulated by them in 1919 when most of them probably seemed somewhat venturesome, and which now in 1929 have received the confirmation which time only can give.

acted violently when at the end of some weeks they were injected a second time with minimum doses, after which they were apparently completely cured.

Following this fundamental work, the recognized field of anaphylaxis has widened and the studies which it has inspired are manifold. The possibility of producing anaphylaxis to all the known proteins, toxic or non-toxic, has been successfully demonstrated, and even in recent times the possibility of an anaphylaxis to non-protein substances (sodium chloride, chloroform, quinine) has been indicated. These investigations, which seemed at first to have a purely scientific significance, have assumed an increasing importance in medicine.

Nevertheless, and in spite of this extension, the domain of anaphylaxis was apparently restricted because of the necessity, that was believed to be absolute, of the establishment of sensitization by the parenteral method. It seemed that the digestive tract would always be able to transform ingested

proteins enough to render them inactive. It appeared, as a matter of course, unlikely that the small intestine would be able in its physiological state, to absorb undigested complex proteins, veritable poisons for the organism.

The works of Arthus and Besredka seemed to confirm this opinion, indicating that the ingestion of proteins could not sensitize animals. However, certain clinical symptoms, especially frequent in infants, quite definitely proved the possibility of alimentary anaphylaxis. The abruptness of symptoms observed after the ingestion of certain foods, the increasing intolerance of certain infants to cow's milk, the marked loss of weight that was suffered when, after having been put back to the breast, cow's milk was taken again—all these facts that have been explained by the word "idiosyncrasies" had many points in common with the symptoms of experimental anaphylaxis.

Since anaphylaxis through the parenteral method has entered the clinical domain only

after having been studied for a long while in the laboratories, it is interesting to notice that alimentary anaphylaxis has been developed by a different method. It is true that this type of anaphylaxis was more difficult to reproduce experimentally. It was only in 1906 that, for the first time, Rosenau and Anderson, by introducing horse serum through the digestive tract, produced anaphylactic sensitization in guinea pigs. Since then Bernstein, Richet, ourselves, Wells, Osborne, and Kleinschmidt have reproduced it with many different proteins.

Alimentary anaphylaxis, therefore, is well recognized in the clinic as well as in the laboratory. Its rôle in pathology is extensive. Its biological rôle is far-reaching. As Richet says, it is very probable that it is active every day in modifying our perpetually unstable state of equilibrium, and in establishing for us a humoral personality as memories and previous sensations create a psychological personality for us. When we realize, moreover, that the state of sensitiza-

tion can be transmitted through heredity, it is evident that the existence of alimentary anaphylaxis raises many possibilities.

Without going too far into this rather philosophical domain, we will discuss in this monograph the clinical and experimental facts relative to alimentary anaphylaxis, and we shall endeavor to indicate its pathogenesis. In these often abstract expositions, we have tried to separate the facts which are apparently well established from those which are still hypothetical.

II. Definition and History

Under the term alimentary anaphylaxis are included all of the reactions arising from a second ingestion of wholesome and normally well tolerated foods which, when first ingested, give mild or no reactions whatsoever.

This definition permits the definite separation from anaphylaxis, on the one hand, of the alimentary intoxications due to the ingestion of decomposed or toxic foods, and,

on the other hand, of certain special susceptibilities which manifest themselves with the first ingestion and do not increase with the following ones. This definition of anaphylaxis includes certain intolerances which after occurring with the first ingestion become more and more violent with subsequent ingestions.

In a recent article we did not include in this definition the reactions observed after the ingestion of certain medicinal substances (bromides, quinine, iodides, antipyrine, mercury). It did not seem justifiable, at that time, to designate such reactions as due to anaphylaxis.

The first studies on this problem were based on clinical observations. Hutinel, Barbier, Finizio, Halberstadt studied anaphylaxis due to milk; Horwitz, Lesné, Castaigne and Gouraud, anaphylaxis due to egg. The following articles described successively the definite manifestations of alimentary anaphylaxis: Doerr, 1908; Madame Bouteil, 1909; Ch. Richet, 1910; Castaigne and Gou-

raud, 1910; Barnathan, 1911; Gendron, 1911; Laroche, Ch. Richet, Jr., and Saint-Girons, 1912; Lesné and Ch. Richet, Jr., 1913; Lesné and Dreyfus, 1913; Laroche, Ch. Richet, Jr., and Saint-Girons, 1914; Weill-Hallé, 1914.

This subject was presented to the Congress of Medicine at Paris in 1912 and reported by Ch. Richet to the Congress of London in 1913.

III. Clinical Facts and Etiology

There are many substances whose ingestion can produce alimentary anaphylaxis.[2] The following is the list, which is undoubtedly incomplete, of sensitizing foods: raw

[2] We feel now in 1929 that all foods except water and sugar may be productive of food allergy. The rôle of wheat, chocolate, potato, and fish has been especially recognized. We think that most chemical products can produce an anaphylactic state, even though they are crystalloids. Our former list of foods is certainly not complete. The three which give clinical symptoms most frequently are, in order of frequency: eggs, especially in children from 2 to 16; milk, especially in nurslings and up to sixteen; wheat products, especially in adults.

meats, cooked meats, milk, eggs, crustaceans (spiny lobsters, lobsters, crawfish, shrimps), mollusks (mussels, oysters), kidney beans, onions, prunes, strawberries(?), pineapple(?), melons(?).

Raw meat, especially that of a horse, cannot produce, properly speaking, an anaphylactic reaction, but it can sensitize the subject so that violent reactions to horse serum will occur (Rist and Ch. Richet, Jr., Lafforgue, Billard) and M. Chauffard reports an unpublished case entirely substantiating this fact. The ingestion of the meat of the hog or cow (well cooked) can give rise to anaphylaxis; Bruck has demonstrated this by means of passive anaphylaxis. Raw milk produces anaphylaxis as easily as cooked milk. All varieties of milk, moreover, can produce anaphylactic sensitization. There is perhaps a co-anaphylaxis or group anaphylaxis to milk; that is to say, that the milk of a cow can, in certain cases, produce anaphylaxis to the milk of a goat or ass. The clinical facts and experiments seem to substantiate

this. In milk itself, whey, casein, and buttermilk have been held responsible.

Anaphylaxis to human milk seems quite possible, although much more rare. Richet decided that anaphylaxis explained the case of a child who could not tolerate the milk of one nurse, but gained when he was nourished by another. There are some infants who lose weight until a nurse whose milk agrees with them has been found. But those mothers whose milk does not agree with their children, nevertheless have a milk of good quality and can nourish other infants. There are some unusual cases where it seems that there is an individual anaphylaxis to the milk of a certain nurse and not for mother's milk in general.

Anaphylactic reactions are often observed following the ingestion of eggs. Raw or half-cooked eggs (eggs in the shell) and poached eggs are much more toxic than cooked eggs (hard boiled eggs in particular). Eggs mixed in flour, as they are in pastry, tarts, dry cakes, etc., are also better tolerated. It seems

that the white and yellow are both capable of precipitating reactions. In other cases, the sensitization is dissociated. Certain persons are sensitive to the white of eggs alone and others (undoubtedly fewer in number) to the yellow. It is not definitely known whether the individuals sensitive to hen eggs are also sensitive to duck eggs. In one case, however, the individual sensitive to the white of hen eggs was also sensitive to duck eggs and in another instance to goose eggs. In fact, the person thus sensitive to hen eggs could eat the meat of a chicken with impunity. Nevertheless, such a patient described by Horwitz had urticaria each time that he ate chicken liver.

Anaphylaxis to crustacea, to fish, and to mollusks, is the most frequent of all types of alimentary anaphylaxis. It is, in certain cases, very markedly specific. The case of Landouzy is particularly interesting in this respect. A patient who could eat spiny lobster and lobster without trouble became ill if she ate a single shrimp. The case of Mer-

tens is comparable. A person who could eat crab became sick whenever he ate crawfish. The following seem to be the most toxic fish in our country: rayfish, mackerel, tuna fish, and salmon. In an unpublished observation which was reported to Dr. Richet by Dr. A., there existed a specific anaphylaxis to gudgeon. As for mollusks, mussels seem to be the most strongly anaphylactic as well as the most toxic at the same time. Moreover, Richet has extracted from mussels a toxin remarkably sensitizing, the mytilo-congestine.

If all of the foods that we have just enumerated are studied in a group it can be stated in general that the proteins which approach nearest to human protein, that is to say the less heterogeneous ones, are the least sensitizing; meat of mammals less than eggs, eggs less than fish, and fish less than crustacea or mussels. Alimentary anaphylaxis is much more rarely provoked by vegetable proteins. Debove has cited a very curious case of anaphylaxis to kidney beans. Castaigne and Gouraud recall apropos to this observation, anaphylaxis to onions. Melon, according to

a case observed by one of us, seems to be equally sensitizing. One of us treated a woman sensitive to a certain number of fruits (cherries and strawberries) in an attack of severe anaphylaxis evidencing itself in the tissues under the eyes thirty seconds after the ingestion of a single prune.

The symptoms of anaphylaxis are especially frequent among children who seem predisposed by the three following conditions.

1. Overfeeding, to which they are frequently subjected.

2. The feeble activity of their digestive juices.

3. The frequency of enteritis.

Alimentary anaphylaxis is often familial; such are the cases reported by Finizio in two brothers, and those of Halberstadt in two twins. It can be hereditary (observations of Gelpke and Laroche).

Medicinal substances whose ingestion can result in anaphylactic reactions are not very numerous. The list of them is confined to the following: antipyrine, quinine, aspirin, veronal, iodides, and bromides.

CHAPTER II

SYMPTOMS

The symptoms produced by all sensitizing substances are nearly identical. However, the reactions vary in intensity—mild, serious, fatal, according to the case—but they always seem to be of the same nature. By careful examination of the facts, it is seen that the reactions of alimentary anaphylaxis are nearly identical with those that are observed after the injection of serum in a sensitized subject, or after the puncture of an hydatid cyst, indicating that there might be a single anaphylactizing poison. It does not seem necessary to us to describe the clinical manifestations of each etiological type of alimentary anaphylaxis.

In this study, following the division that we proposed in 1912, and which was adopted in 1913 by Lesné and Dreyfus, and by Ch. Richet in our report to the Congress of Lon-

don, we will describe in order the general symptoms[1] observed in:

(1) severe alimentary anaphylaxis;
(2) mild alimentary anaphylaxis;
(3) chronic anaphylaxis;
(4) hereditary anaphylaxis.

I. Severe Alimentary Anaphylaxis

Severe alimentary anaphylaxis has been observed especially after the ingestion of eggs, mussels, and milk.

The observations of extreme hypersensitiveness to eggs can be grouped in two large classes; the first class includes the observations of Lesné, of Gelpke,[2] of Landmann, of Schoffield, and of Horwitz (the first three in

[1] The division of the symptoms of anaphylaxis into two great classes, the little "a" and the great "A" indicating the mild and the severe symptoms, has been followed by most authors in France and in Italy (Pagniez, Sales and Verdier, Drago).

[2] The etiology in the case of Gelpke is particularly curious. It concerned a child of nine years, convalescing from measles without complications. Following a bath containing two raw eggs, he presented a scarlatinoid exanthema with

children and the last two in adults). These are definitely cases of anaphylaxis. The second class, which includes the observations of Baginski, of Faust, and the two cases of Guinon (cited by Barnathan) indicate the establishment of intolerance after the first ingestion of egg. Is it a question then of simple intolerance or of hereditary anaphylaxis? The question is unsolved at the present time. At present we will be concerned only with the phenomena of the first group.

It is remarkable that the beginning of the reaction occurs sometimes fifteen to thirty seconds after the ingestion of a minimum quantity of a preparation containing ovalbumen. The patient of Landmann, a very vigorous man of thirty-five years, developed extremely intense urticaria, and Horwitz stated that the immediate reaction in his

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edema of the face. At the same time he was taken with dyspnea and pain without having any fever.

The mother, when questioned, stated that each time her son took eggs, he broke out with urticaria and had diarrhea and severe abdominal pains. She herself had the same reactions after each ingestion of eggs.

patient proved an actual protection against a fatal reaction by preventing him from finishing his drink. Usually the reactions appear a little later—two to three minutes; in the case of Lesné, ten minutes; in other cases, as reported by Horwitz, fifteen to forty-five minutes.

This rapid onset of reactions is one of the many characteristics of anaphylaxis. In regard to this, Horwitz states that those reactions which are rapid in onset produce the most serious consequences. The first symptom is usually urticaria, which develops rapidly, or many violent paroxysms of colic and vomiting. The symptoms reach a climax quickly. At this stage we have a complete clinical picture with the following symptoms:

Cutaneous; digestive; respiratory; nervous, with a serious general condition.

Urticaria is very frequent and of an extreme severity. In the four principal observations (Lesné, Landmann, Schoffield, and Horwitz) it occurred three times. It is more marked in the face, particularly in the lips, in

the eyelids, etc. The itching is very distressing. Occasionally a scarlatinoid exanthema is noted (case of Gelpke). The digestive symptoms together with urticaria constitute the essential phenomena of the anaphylactic reaction. Colic is very severe and so characteristic that the patient of Horwitz called it by the name of "Eierbauchweh." The little patient of Lesné writhed on the ground crying out with the attacks. Diarrhea is rarely absent. Most often, it is very marked, sometimes uncontrollable and even bloody. Vomiting, preceded by nausea, is very frequent and may be of such severity that even liquid cannot be taken. Most often the abdomen is contracted and depressed. More rarely, other symptoms are observed: dyspnea (Lesné) or even a real asthma (Schoffield), spasms or convulsions (Schoffield).

At the same time the general condition is aggravated, the temperature may fall to 36° C, though more often it is raised. The blood pressure is lowered, the eyes are hollow, the nose is pinched, the face becomes

livid, and the patient may become prostrated or torpid. These severe symptoms are infrequent and seldom occur in the clinical picture. Their duration is variable. Urticaria and abdominal pains rarely last more than seven to eight hours. Occasionally, however, the reactions are prolonged and the patient can, according to the observations of Lesné, be uncomfortable for many days.

The following are observations reported by Landmann, Horwitz (Observation II), Schoffield, and Lesné, the last two in children.

Landmann's observation.—This concerned a man of thirty years who presented a specific idiosyncrasy to egg protein. The family history was negative. The patient had been nursed by his mother. When he was one year old he received a small quantity of egg in his soup for the first time. The egg upset his digestion, and discomfort recurred with each successive trial. At the age of nine years, after the ingestion of egg albumen, some cutaneous manifestations occurred for the first time. Actually a trace of egg, scarcely

perceivable (such as a frosting which had been clarified with the white of an egg) was sufficient to produce an intense urticaria with alarming symptoms resembling those of poisoning.

Landmann on one occasion gave his patient an amount as large as a pea of a special preparation, which unknown to the patient contained some egg albumen. Some seconds after this the man developed a sensation of a severe burning (an edematous erythema appeared on his tongue) in his mouth and on his skin. His eyes watered. His ears buzzed. Violent vomiting occurred, and at the end of fifteen minutes severe diarrhea occurred, accompanied by a sensation of burning throughout the length of his digestive tract. The diarrhea was uncontrollable for many hours, and it was only by degrees that the symptoms became less severe.

Horwitz's case.—A man of sixty years became sensitized at the age of five years to egg. This sensitization increased and was at its maximum between the twentieth and the

fortieth years. One-quarter to three-quarters of an hour after the ingestion of the smallest quantity of egg imaginable, the patient was taken with gastric cramps comparable to nephritic or hepatic colic and with extremely severe localized pain which the patient called "Eierbauchweh."

At the same time there developed vomiting and diarrhea, which, moreover, failed to relieve the symptoms. A sensation of general discomfort with a faint and rapid pulse developed and the clinical picture recalled that of an intoxication. These reactions lasted from seven to eight hours. In old age the reactions are the same as in middle life, perhaps even more violent.

Lesné's case.—This concerned a little girl of eight years who had over-eaten and who ate a fresh egg every morning for her breakfast. For a long time this child only had symptoms of dyspepsia; then she had from time to time some urticarial lesions and some areas of facial edema. After this period of tolerance, or rather intolerance, more serious

reactions appeared. Each day, during her breakfast, the child complained of violent abdominal pains; she rolled on the floor, vomiting. She became pale and her extremities grew cold. The reactions lasted from fifteen to thirty minutes, then disappeared, and the child in the evening was entirely well. Successively, it was decided to be a question of appendicitis, of cyclic vomiting, of poisoning. Finally some one thought of egg intoxication. Eggs were taken away and the reactions disappeared.

One day, many months afterwards, unhappy because her daughter could not eat eggs, the mother gave her a few spoonfuls of egg in her coffee and cream. This food was hardly ingested when the child was instantly taken with the most terrible symptoms, worse than ever before. She rolled on the floor, complaining of violent abdominal pains, her stomach contracted, her eyes were hollow, her face became livid and choleric, dyspnea appeared, her temperature was lowered to 36° C, her pulse was imperceptible,

her arterial tension was lowered, her gastric intolerance was complete, the violent vomiting became incessant, and diarrhea also appeared. This particularly serious condition, which threatened immediate death, persisted for some days, and the child could be revived only by active therapeutic measures. After abstaining for many days, the ingestion of minute quantities of egg in the form of cakes caused new crises to appear, less serious and less prolonged than the first.

The little patient of Castaigne and Gouraud presented identical symptoms; after four to eight drops of egg yolk, terrible colic with diarrhea appeared.

Schoffield's case.—A child of thirteen years who became ill after each ingestion of egg, no matter how minute the quantity, was afflicted with a cutaneous urticaria and severe mucoid expectoration, asthma and convulsions.

No fatal case of anaphylaxis to eggs has been recorded up to the present, though the symptoms frequently have been very alarm-

ing. The little patient of Lesné was near death for some days. The elderly patient of Horwitz, from his own statement, would have died if he had finished his egg albumen. Landmann's patient seems to have been in a still more serious condition from a still smaller dose. As for the prognosis, it must be withheld; it is more unfavorable as the reactions become more rapid in their appearance, more intense in their development, and more prolonged in their evolution.

Anaphylaxis to mussels is very frequent, for, along with reactions of a directly toxic or infectious order, affecting many persons at the time, is cited the idiosyncrasy to mussels, peculiar to certain individuals. However, the observations already published are quite rare. It is probable that they will become more numerous as greater professional interest is displayed in them.

Personal Report of Dr. Ledent—

After having eaten some mussels three years ago, I was taken with a feeling of suffocation and a sensation of dryness and irritation in the back

of the throat. These various marked symptoms manifested themselves twenty minutes after the ingestion of this food, which heretofore had never caused either indigestion or illness. Let us state that none of the guests was affected.

Fifteen days later, the same repast produced the same symptoms with more violent headache, hives and diarrhea. I recognized the cause of the symptoms because it was some time since I had included mussels in my diet. Because of the severe manifestations, even though the food had been taken in the minutest amounts, I thought of anaphylaxis. I have eliminated mussels from my menu for a year, I have never used them since, and I no longer have any cause for complaint.

In 1912, Flandin and Tzanck reported an observation whose anaphylactic nature was demonstrated by passive anaphylaxis. It concerned a man twenty-six years old who purposely, at the end of January, 1912, ate some mussels for the first time in his life. The fourth of March he ate some more. On the following night the patient developed a severe illness, with vertigo and dyspnea. On the morning of the fifth, there appeared on his skin a red and pimply eruption. On the

tenth he consulted Monsieur Darier, who diagnosed it as generalized urticaria. With the serum of the patient, it was possible to demonstrate passive anaphylaxis in the guinea pig.

Case observed by Chauffard and Flandin (unpublished).—This concerns a woman of twenty-six years, who on the seventeenth of December, 1912, ate a plate of mussels for lunch. She had often eaten them without discomfort and she did justice to the dish that was served. Twelve hours after, at midnight, the patient was awakened by generalized abdominal pains. She got up and was taken with dizziness. She had disturbed vision, buzzing in the ears, and then vomiting at first gastric and then bilious in type. The vomiting was painful and was preceded by nausea and the vomitus had an offensive odor. Some remains of undigested mussels were found. The patient presented in addition to this an abundant and offensive diarrhea (six to seven evacuations a day). For two days she had a definite weakness, a very marked degree of

asthenia with a hyperesthesia of the entire abdominal region, but no cutaneous eruption and no itching. At the end of two days the patient went back to work, having only a little residual pyrosis, some sensation of puffiness in her mouth, and a fetid breath. She had a distaste for no kind of food except for mussels.

On the twenty-fifth of December, 1912, the people for whom the patient worked out as a seamstress gave her some mussels for breakfast. She dared not refuse but, mistrustful, she ate only two of them this time. Three hours after, she was seized with vomiting, preceded by vertigo and by syncopal tendencies. This vomiting was very profuse, first gastric, then bilious and very fetid. The patient had, in addition, some diarrhea which was itself extremely fetid and was accompanied by intestinal and rectal tenesmus. This condition lasted many days.

The history of this woman is typical in many respects; it was a case without doubt of hypersensitiveness acquired by the patient

who had not been sensitized previously. Was the first crisis due to anaphylaxis? We cannot say, but everything points against it: the large quantity of mussels ingested, the late onset of the reactions. It was a question then, probably, of ordinary indigestion, produced by her susceptibility to mussels. The second time, only two mussels brought on the symptoms which occurred sooner (three hours). Here the anaphylactic reaction definitely appeared.

Susceptibility which suggests indigestion is a common occurrence. One of us was able to study the following case.

A man sixty years old who was perfectly tolerant to oysters and of which he was very fond became completely intolerant to them (vertigo, nausea, immediate vomiting) following indigestion from oysters occurring at the age of forty. Since that time he cannot tolerate a single oyster and has been obliged to eliminate them from his diet.

Certain fish can produce violent anaphylactic reactions. Dr. A. has given us a record

of his own case. Up to the age of twelve he was able to eat gudgeons. One day he was taken with profuse vomiting, pains, faintness, colic, and diarrhea after a meal including this fish. All distress had disappeared in forty-eight hours. One of his friends who had eaten the same dish was not sick. The same attacks recurred many times afterwards.

Among children, anaphylaxis is characterized by a few definite symptoms. Among nurslings, anaphylaxis to milk or buttermilk is recognized in the articles of Hutinel and Barbier, who were the first to draw attention to these symptoms. Since then, observations have been multiplied, but their value is less important. We will mention those of Freund, Siegert, Wernstedt, Zybell, in Germany; those of Fiessinger, Dufour, in France; and we will retain in this discussion of etiology only those of definite value. Such are the cases of Finkelstein (two observations), of Salge, of Halberstadt, of Hutinel (two observations), of Finizio and of Zybell. As Hutinel re-

marks, they seem to be copied one from the other. In three of these observations, the reactions were terminated by death.

Finkelstein's case.—This case is that of a nursling, who gave reactions every time that he received cow's milk. At each trial (fifth, ninth, and eighteenth weeks) the symptoms were more severe; and when at the twenty-sixth week a last trial, as a result of an unwise persistence, was attempted, death resulted from collapse.

Finizio's third case.—The following case is similar to the above. A sickly child, rachitic, tubercular, and breast fed, took some animal milk during a previous stay at the hospital. At one year of age, he was given a bottle containing 120 grams of milk. Two to three hours after, serious symptoms appeared — intestinal vomiting, followed by frequent mucous, and fetid diarrhea with tenesmus, dyspnea, uncountable pulse, and marked depression. Eight days later, a second trial was followed by similar reactions. Trials with buttermilk, canned milk, milk,

and farina still brought on reactions, though less serious. Two months after, the child was given 100 grams of milk; the symptoms appeared immediately—vomiting, bloody diarrhea, dyspnea, cyanosis, convulsions, and death. No autopsy was performed. It is interesting to note that the younger brother of this child likewise exhibited alimentary anaphylactic reactions to milk which were nearly fatal.

Halberstadt's third case.—This case deals with a child born prematurely who was breast fed and had supplementary feedings of buttermilk. He was unable to tolerate buttermilk and on two different occasions some slight reactions were observed after taking it. Some time after, at the age of three months, the child took buttermilk again. Four hours after, he went into a collapse. The following day he was revived with difficulty and although he was given mother's milk, depression and death occurred. An interesting detail was the fact that a twin brother of this child presented some very serious anaphy-

lactic reactions to milk which likewise resulted in death.

The cases detailed above present marked general symptoms. In chronic cases, on the contrary, the digestive symptoms are the most marked. Vomiting and diarrhea are prominent in all the cases; the diarrhea can be glairy (Hutinel) or bloody (Finizio). It is often very frequent (seventeen stools in the case of Hutinel) accompanied now and then with rectal tenesmus. The general symptoms vary in intensity. In mild cases prostration is common; it is more marked in serious cases and results in collapse. High temperature (up to 40° C) is frequent. Low temperature is uncommon (34.4° in the case of Salge).

Frequently convulsions, tetany (Halberstadt, Finizio), albuminuria and dyspnea occur. These reactions which come on immediately after the ingestion of milk persist for a certain time and many days elapse sometimes before every trace of anaphylactic reaction disappears. As we have stated, in

three cases, death has been observed; in many others it has been imminent. Moreover, the prognosis in alimentary anaphylaxis to milk must be guarded.

The following are cases reported by Zybell, Finizio, Hutinel, and Salge.

Zybell's observation.—A child of three years, entirely breast fed until then, received 100 grams of sweetened cow's milk diluted one-half with water. He soon had copious and repeated vomiting and remained pale and prostrated with a feeble pulse and superficial respiration for many hours. The stools were frequent but of normal appearance. The following day, the temperature was 39.5° C and fever lasted three days, the child losing 40 grams in weight daily in spite of taking the breast well. Eight days later, a new trial resulted in the same symptoms (vomiting, collapse, feeble pulse, superficial respiration, fever of 38.7°, stools oily and clear, no loss of weight). Fourteen days after, when all the serious signs had disappeared, 20 grams of a mixture of cow's milk

and mother's milk, skimmed by centrifugation, were given. Vomiting, collapse, fever of 38.4°, loss of weight of 160 grams, resulted with a return to normal at the end of 24 hours. A week later, 4 grams of buttermilk without salt with 100 grams of centrifuged mother's milk were given and resulted in slight thermic elevation (37.6°). Later, small amounts of cow's milk could be taken with little discomfort. Death occurred later from a pulmonary affection.

Finizio's Cases, I, II, and IV.—Case I. A normal infant that had previously been nourished at the breast went to the hospital because of green diarrhea, but in good general condition. Upon entering the hospital his mother gave him a glass of cow's milk and immediately there appeared vomiting, diarrhea and convulsions. At each new trial the symptoms recurred.

Case II. Finally a younger brother, aged seven months, feeling well up till then, showed a similar reaction from the first feeding of cow's milk. He was taken with vomit-

ing and fever with tetany. On examination of the serum some precipitins were found.

Case IV. Another observation dealt with a child of six months, a brother of the one who died from anaphylactic reactions and whose history we have already studied. He showed, from the first ingestion of cow's milk (twenty grams), immediate vomiting and prostration.

At each new trial, the same symptoms recurred even more accentuated. When he took a spoonful of milk soup, he was afflicted with vomiting, prostration, diarrhea, and a tendency to low temperature. During these crises, he had no albuminuria. Precipitins to cow's milk but not to mother's milk were found in his serum. At the end of some weeks of anti-anaphylactic treatment, the symptoms disappeared.

Hutinel's cases—

"I have observed many patients suffering from severe colitis (dry cholera) who, when improved by treatment and rigid diet, devel-

oped severe symptoms of toxemia, following one or two spoonfuls of milk. The eyes became sunken with dark brown circles, the nose became pinched, the face took on a pale or livid appearance, the extremities became cyanotic and erythematous, and urticarial eruptions appeared on the face, the arms, the limbs, and the buttocks. The stomach became scaphoid, the large intestine contracted and was cordlike to palpation; the stools soon became glairy or bloody and nervous reactions frequently developed.

"I recall particularly one of these children. I had talked to the mother about giving him milk. The attending physician believed it necessary to give some of it to him by injecting it into the bowel. Some acute symptoms resulted from this unfortunate intervention.

"I have been taking care of a beautiful little girl of eight years since her birth, who has had a serious entero-colitis and has become, because of this fact, absolutely intolerant to milk. One day her mother risked giv-

ing her a spoonful of coffee with cream. Almost immediately afterwards, the child vomited and in the night she had seventeen glairy stools. Later she had an extremely long and serious attack of typhoid fever; it was impossible to make her tolerate cow's milk, but fortunately she could digest goat's milk.

"I have seen a beautiful little girl of eleven months in whom digestive symptoms occurred when, at the age of nine months, she was given boiled cow's milk in two nursing bottles containing fifty grams each. After this unfortunate experiment the child was nourished exclusively at the breast and throve until her nurse suddenly left her. She was given a hundred grams of cow's milk. Almost immediately, she was taken with vomiting, diarrhea, and prostration and I advised her to get another nurse immediately. My advice was heeded and the symptoms disappeared."

Salge's case.—An infant was at first nourished at the breast. The second of Janu-

ary a mixed formula was administered at the orphanage and the child was weaned the first of February. It was taken away and after three weeks was brought back with dyspepsia. It was put to the breast again the twenty-eighth of February and it seemed cured. At nine o'clock in the morning it was given sixty grams of cow's milk. At noon collapse, cyanosis, and a rectal temperature of 34.4° resulted. It was revived with mustard baths, some injections of camphor oil and hot blankets and it was put back on the breast on the following day. At the end of the eleventh of May, it was given some buttermilk which it tolerated quite well, and it was finally taken away from the orphanage.

Thus, in nurslings, anaphylaxis to mother's milk, cow's milk, and buttermilk exists (observation of Halberstadt). Its principal characteristics at this age are, on the one hand, its serious nature, and on the other, certain special symptoms such as tetany and convulsions.

II. Mild Alimentary Anaphylaxis

Along with severe anaphylaxis there exists what we may call a mild alimentary anaphylaxis which does not produce severe and dramatic attacks (which it is important to state is exceptional) but slight reactions whose nature can be recognized only by the most careful inquiry into the patient's régime. The sooner these reactions are grouped into a syndrome the sooner they are isolated and finally they constitute a true dissociated anaphylaxis.

These reactions are very frequent and usually mild. They can be observed in adults who have presented a slight intolerance to certain foods from their infancy. However, they frequently occur in a tolerant person after overeating, for example, during convalescence. They also appear in children whose diet has been increased too suddenly. The most frequent and most marked cases among children are those of intolerance to milk or to eggs.

The intolerance of infants to cow's milk can actually be manifested not only in sudden dramatic anaphylactic reactions but by mild reactions of an analogous but prolonged type. The infant who is sensitive to cow's milk may develop cutaneous reactions such as erythema or eczema and also at times diarrhea or vomiting and a progressive loss of weight. This group of symptoms may be continuous or may occur in crises so long as milk is administered. Thus it may develop into what we have called chronic anaphylaxis. Between these two groups there is only the question of intensity of symptoms.

M. Barbier, who was one of the first to recognize the anaphylactic nature of these reactions, made a clinical observation the interpretation of which is somewhat uncertain. It dealt with an infant of six months, fed on cow's milk, who developed eczema and vomiting after each ingestion of this food. When cow's milk was replaced by goat's milk, the eczema disappeared, his weight increased, and the vomiting ceased. Some time after,

M. Barbier gave him thirty grams of goat's milk mixed with the cow's milk. The child had vomiting and diarrhea as a result of which both symptoms disappeared with a return to goat's milk.

Anaphylaxis to eggs is still more frequent. Over a period of months, a child (between the ages of three and five years) took two or three eggs a day. The tolerance was perfect at first but little by little some symptoms appeared. These were gastro-intestinal disturbances, such as fetid breath, chronic dyspepsia, constipation, frequent loose stools, along with cutaneous manifestations such as urticaria, prurigo, and eczema. The urticaria which at first diminished after each meal soon became chronic. Wheals occurred on the arms, the thighs, or the sides, and the scratching which they occasioned resembled the crises of itching seen in eczema or cutaneous infections. Sometimes edema of the face, of the eyelids, or more rarely of the limbs occurred. When the alimentary origin of these reactions was recognized the relief of the symptoms was

generally very rapid, but the symptoms reappeared when the food which caused them was eaten again. Among these reactions there are those which are positively due to anaphylaxis; others are of disputable pathogenesis. In the first group can be included urticaria and attacks of itching and of edema. The proof of this is that the children who have presented reactions brought on by certain foods sometimes keep a specific sensitization to them even when an appropriate diet has eliminated all chronic intoxication. Thus, one of us has observed a child who, at the time of weaning, was fed on egg every day or two. Certain gastro-intestinal symptoms appeared, together with itching and attacks of urticaria. As soon as eggs were kept away all the reactions disappeared only to reappear as soon as eggs were eaten again. Two years afterwards, the child still possessed a specific sensitization to eggs which was evidenced by urticaria, even though the intestinal disturbance had been absent for a long while. When care was taken to serve the yolk of the egg

entirely separated from the white, the child evidenced no trouble. It was therefore a definite question of a specific sensitization to ovalbumen.

Two symptoms, however, asthma and urticaria, when they appear isolated, must be considered of a possible anaphylactic nature. It is to such manifestations that the word "dissociated anaphylaxis" can be applied. Certain asthmatic cases have been shown to be due to anaphylaxis. The patient of Schoffield had attacks of asthma after the eating of eggs. Madame Girard-Mangin has published two cases of asthma of anaphylactic origin in an old man and in a child. These facts support the anaphylactic theory of asthma proposed by Billard and Landouzy.

Lesné and Ch. Richet, Jr., think that certain cases of migraine in old age are due to anaphylaxis. Other authors attribute cyclic vomiting to anaphylaxis.

But urticaria especially should be considered of anaphylactic origin. Certainly we

do not wish to state that all urticaria is of anaphylactic origin, but its sudden onset, its repeated appearance after the ingestion of specific foods, its recurrence in a limited group of people are all in favor of making us consider it an anaphylactic reaction. The following is an observation of Brazis (of Mulhouse) which in many respects is particularly interesting.

Brazis's case.—Madame J. B—— had never had any distaste or intolerance either for milk or for eggs. Soon after her marriage and before the birth of her first child, probably during her pregnancy, she noticed, without attaching the least importance to it, a sensation of burning and a slight eruption on her lips as soon as she took cream.

Three weeks after her first confinement, the first day she went out, she lunched very simply on chops, vegetables and a lettuce and egg salad. She had hardly eaten when she was taken with suffocation and sensations of burning from her head to her feet and was obliged to go to bed. These phenomena re-

curred each time that she took eggs and the severity of them steadily increased. At first she could tolerate the yellow of the egg, the white alone producing the reactions, but little by little the yellow itself became injurious to her. It is more than probable that these reactions which followed the ingestion of the yellow of the egg were due to some inappreciable particles of albumen adhering to the yolk of the egg.

Attributing these phenomena of intolerance first to imagination or to auto-suggestion, then to a questionable freshness of the eggs, she tried time after time to reason with herself and to take only eggs of indisputable freshness, but she was obliged to abandon radically all tentative experimentation for the effects of the intoxication recurred with a violence and a rapidity nearly dumbfounding. Even the ingestion of the smallest particle of egg, a mere trifle of sauce or of pastry containing egg, immediately produced tingling in the throat and ears, then all over the body, from her head to the soles of her feet

and internally all through the digestive tract. The only time she defied her susceptibility she took an egg, whole and fresh, fourteen or fifteen years ago, and remembered having had especially large swellings of the skin and some pustules, besides all the other phenomena of this strange intoxication, such as vomiting, intolerable itching, etc.

After the birth of her second baby, encouraged by some people who assured her that the second pregnancy would modify this sensitization to egg, she experienced another reaction. Without warning her, the mother put a quarter of an egg yolk into her lentil soup and she immediately succumbed to her intolerance, although she was assured that egg was not the cause. She tried to endure it, wishing to continue her dinner, but in vain, the reaction had begun. Itching, nausea, vomiting, and intolerable pain continued until midnight.

She risked a last experiment four years ago after typhoid fever, thinking without doubt that this illness might possibly have

removed her unfortunate susceptibility. It was not successful.

This lady adds that her children fortunately have not inherited her intolerance to eggs but her solicitude for them has permitted her to make two other equally curious observations. When handling or opening eggs in the shell for her children, she inadvertently brought her fingers to the eggs and touched her eyelids without having previously washed her hands. Her eyelids became inflamed immediately and caused her unendurable itching for at least two hours.

Finally, three years ago, while opening an egg at both ends with a pin in order to make one of her children drink directly from the shell, she pricked her finger slightly with this pin. The wound was so insignificant that she did not attach any importance to it but she noticed some moments later, at the point of the prick, a little white and hard swelling like a hive which disappeared without further disagreeable results. The violent irritation of the eyelids from contact with a trace

of albumen and the appearance of a papule immediately after an insignificant prick with a pin whose point had been moistened in egg white are phenomena comparable to those which the skin reaction to tuberculin presents.

The duration of alimentary anaphylaxis is not known. There are certain subjects, sensitive in early infancy, who are still sensitive at the age of sixty—for example, the patient of Horwitz. One of us has observed a subject still sensitive at the age of sixty-three. However, in general, the anaphylactic state diminishes in intensity and may disappear with increasing age. Such was the case already quoted in a patient with an anaphylaxis to gudgeon.

Thus anaphylaxis, particularly that to milk, may not persist in adult life. Moreover, as we shall see later, anti-anaphylactic treatment succeeds to a certain degree in shortening the duration of this anaphylactic state.

III. Chronic Anaphylaxis[3]

This section contains helpful data in regard to certain allergic reactions produced by cow's milk. In general it deals with infants who are overfed, underfed, or obese, and who have indigestion and large viscous stools. These symptoms usually occur in three definite stages in the patient. First, there is a phase of gastro-intestinal strain due to overeating; the weight may increase rapidly; the child may even become obese before the first anaphylactic reactions occur; second, there occurs digestive intolerance with stools of abnormal appearance and with stationary weight; it is perhaps at this phase that the overworked digestive tract incom-

[3] Chronic and hereditary anaphylaxis of which we previously in 1919 spoke with cautious reserve is now classical. The symptoms of food anaphylaxis have, among many others, these three characteristics: (1) They are always the same in the same patient (although they vary in mildness or severity); (2) they may be quite different in two patients, although the food which produces these pathological states is the same; (3) similar symptoms may result in the same patient from different foods.

pletely digests the proteins which pass into the blood and sensitize the organism; third, the phase of anaphylaxis occurs with cutaneous (erythema, eczema), digestive (diarrhea, vomiting), or general manifestations (growing thin, sometimes markedly so in a few days). The latter phase lasts as long as the diet is not modified.

When cow's milk is taken away and replaced by mother's milk or by farina, the reactions often disappear, the general condition improves, and weight increases. If the use of cow's milk is persisted in, more serious symptoms develop, digestive troubles arise, and death may occur through cachexia or associated infection. Relief is obtained only with absolute exclusion of cow's milk and the feeding of mother's milk or farina.

Only to a certain degree can one admit the anaphylactic nature of these symptoms. Hutinel and Barbier ascribe this origin to them and their reasons have already been presented. One of us (Ch. Richet, Jr.) has tried without success in some unpublished ex-

periments made with Maillet, to demonstrate the anaphylactic origin of certain gastro-intestinal disturbances through humoral reactions. It is probably necessary to make a distinction among these clinical cases. A certain number of these nurslings are evidently only dyspeptics who digest cow's milk with more difficulty than mother's milk, and, as the cause of such cachexia, insufficiency of assimilation and toxic infections of digestive origin are found. In others we must admit the anaphylactic nature of these reactions, especially when after a varying period of taking mother's milk or farina, the ingestion of cow's milk even in a minimum quantity (as in the observation of Barbier already quoted which agrees with these facts) provokes immediate vomiting, diarrhea, and crises of urticaria. In accord with this, Wernstedt states that the anaphylactic reactions to cow's milk originate most often among nurslings who are bottle fed before being breast fed and who are again given artificial feeding. The first period of alimen-

tation with cow's milk corresponds to the sensitization of the organism (preparatory ingestion) and during breast feeding the anaphylactic state is developed. Finally, when cow's milk is given anew (reaction producing ingestion) anaphylactic shock is produced.

Loss of weight seems to us an important symptom of this chronic anaphylactic intoxication. It is always observed after violent anaphylactic shock, and we have laid stress upon it after many recurrences of emaciation in experimental alimentary anaphylaxis to eggs and milk, showing that, as a whole, the thinnest animals were the most anaphylactic.

Thus, in the clinic, even after setting aside a large number of cases of obscure pathogenesis, there remain certain ones to which we have applied the term chronic anaphylaxis. Though these two words appear at first to be contradictory, it is usually true that anaphylaxis occurs as an acute and violent condition after the second injection of an antigen.

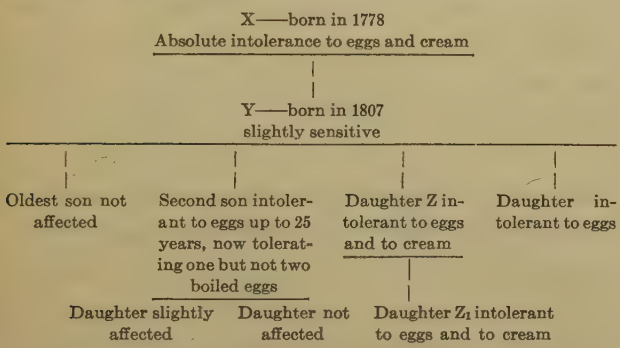
To this acute alimentary anaphylaxis it is wise, we believe, to add chronic anaphylaxis, characterized by the daily introduction of heterogeneous proteins in doses combining each time with antibodies and producing in the organism a series of slight intoxications whose repetition results in more or less serious reactions instead of a definite anaphylactic shock.

IV. Hereditary Alimentary Anaphylaxis

The susceptibility of many members of the same family to eggs and milk is well known clinically. Such cases of sensitization seem to us to indicate anaphylactic pathogenesis. In these cases there may be an intolerance to a very small quantity of the ingested food. Such food may act as a poison producing a rapid sometimes violent immediate reaction.

One of us (Laroche) has observed an unusual history of hereditary susceptibility to eggs. The most marked sensitization was

in the great-grandfather. A cream or a meringue poisoned him. He had given up eating eggs since they produced vomiting, colic and diarrhea. The following is a chart of the family history that we have obtained.


X——born in 1778
Absolute intolerance to eggs and cream
Y——born in 1807
slightly sensitive
Oldest son not affected
Second son intolerant to eggs up to 25 years, now tolerating one but not two boiled eggs
Daughter Z intolerant to eggs and to cream
Daughter intolerant to eggs
Daughter slightly affected
Daughter not affected
Daughter Z1 intolerant to eggs and to cream

The intolerance of X remained legendary in this family. It was said that eggs poisoned him. His son had retained only a special susceptibility to cream and especially to meringue from the beaten white of eggs, either uncooked or partly cooked. To the daughters of Y, eggs were poisonous. Z had some definite attacks of vomiting after the ingestion of cream and she could tolerate only the yolks of the eggs.

The mother of the child observed by Gelpke was sensitive to eggs. Halberstedt's case and Finizio's two cases of anaphylaxis to milk are comparable in having a familial intolerance. Other examples of such history could be cited. Their interpretation is more difficult. Physicians explaining such a reaction have called it "idiosyncrasy." Can we name it "anaphylaxis"?

The reactions which occur among these patients are identical with those we have already studied. They differ from them only in one respect—heredity. But experimental hereditary anaphylaxis has been demonstrated for a long time. If hereditary alimentary anaphylaxis exists, its mechanism is very obscure. It is entirely a problem of humoral heredity. The transmission of this susceptibility through men (case of Gelpke) increases the obscurity of the problem. Its discussion would lead us too far. Let us confine ourselves, therefore, to recording facts.

CHAPTER III

BLOOD VASCULAR REACTIONS

The modifications of the blood resulting from alimentary anaphylaxis have inspired a number of researches (Richet, Richet and Lassablière, Widal, Abrami, Brissaud and Joltrain, Pagniez and Pasteur, Vallery-Radot, J. Héran, and Fr. Saint-Girons.)

Richet has especially studied the leucocytosis in experimental anaphylaxis to crepitine in the dog. From the fourth to the sixth hour after a "reaction producing ingestion" leucocytosis mounts, the normal count being from 100 to 158 (an average taken on 22 dogs), whereas a "preparatory ingestion" only produced a leucocytosis of 132 (average taken on 8 dogs). Widal and his students found in man a leucopenia of 5,000 to 2,000 within a minimum period of five hours after a meal. In addition to this leucopenia, a relative hyperleucocytosis followed. Biedl

and Kraus, in parenteral anaphylaxis have also observed that the shock produces a leucopenia followed by a leucocytosis in the dog.

On the other hand, certain disturbances in the coagulability of the blood exist in alimentary anaphylaxis. M. Widal has demonstrated hypercoagulability in one of his patients. It is true that in parenteral anaphylaxis anaphylactic shock is accompanied by hypercoagulability (Richet, Arthus, Marcel Bloch, Biedl, and Kraus). Thus blood modifications (abnormal coagulation and leucocytosis) are not always identical in the same conditions. These differences depend, perhaps, on the nature of the antigen, the manner of introduction, and the intensities of the reactions.

Finally, a very marked hypotension sometimes has been observed by all the authors.

To this group of blood modifications, M. Widal gives the name of hemoclastic crisis in order to indicate and specify the abrupt character of these blood changes.

CHAPTER IV

EXPERIMENTAL STUDIES

The problem of experimental alimentary anaphylaxis was studied by Richet in 1902, but it is necessary to include the experiments of Rosenau and Anderson in 1906 with horse serum, and of Richet with crepitine, in order to affirm the existence of this condition. Previously, Arthus, Besredka, and others had, it is true, obtained positive results with milk and eggs, but by means of subcutaneous injections. There was a definite anaphylaxis to foods, but no alimentary anaphylaxis.

Rosenau and Anderson fed some dried serum of a horse to guinea pigs. They afterwards injected these animals with a large dose of horse serum. Among 9 guinea pigs there was one death (in 55 minutes); 7 guinea pigs were sick, and another did not develop any symptoms. The existence of alimentary anaphylaxis was thus established. Not only

horse serum but horse meat can produce an anaphylactic reaction. In 23 guinea pigs thus fed and observed following the injection of horse serum, there was one death, 10 were unharmed, and 12 recovered after developing some symptoms. A small number of experiments were made in feeding beef to some of the animals, but the results were uncertain, for guinea pigs do not tolerate beef very well, even though it is mixed with their usual food. These results are, as Rosenau and Anderson themselves have said, open to another interpretation, since the quantity of serum necessary to sensitize a guinea pig is so extremely small (about 0^{cc}.000001), that any erosion of the mucous membrane would perhaps be sufficient to allow the passage of this small quantity of antigen into the blood.

In 1909 Besredka tried to sensitize guinea pigs by oral or rectal feeding, but without success. Although this apparently was a complete failure, Besredka was able to desensitize some sensitized guinea pigs by giving them a little milk either by rectum or by

mouth, which indicated that certain antigens had been absorbed through the digestive tract without having undergone the chemical modifications which make them lose their anaphylactizing properties.

Nobecourt tried to produce experimental alimentary anaphylaxis with the white of egg in a rabbit and obtained some interesting results to which we will return presently. In this same year, 1909, Bornstein fed veal lens protein to some rabbits and he found that sudden death occurred in certain animals from what he considered anaphylactic reactions; but it is impossible to decide from these experiments whether or not death was due to anaphylaxis.

Richet, with the subcutaneous injection of crepitin, a strongly anaphylactizing toxin, obtained some conclusive results in 1911. He demonstrated that there was an alimentary anaphylaxis to crepitin whether it was given by a "preparatory" or a "reaction producing ingestion."

This alimentary anaphylaxis is frequent. It can be serious and it may persist a long time (one year or longer). With the normal diet, less marked results occur. Richet obtained a very positive result in the dog with meat juice and a very slightly positive result with ovalbumen. But seven other dogs who were fed raw meat, eggs, or milk did not develop any symptoms at the time of investigation.

About the same time Arthus and Besredka were unsuccessful in their experiments. On the contrary, we have obtained some positive results. We fed guinea pigs a diet composed exclusively of a mixture of bread (150 grams) and milk (900 grams) for many days. Under such conditions we have been able to establish anaphylactic sensitization in our animals in a proportion of from 25 to 80 per cent, according to the series.

Anaphylaxis to boiled milk as well as to raw milk lasts for some minutes. In animals sensitized by the feeding of cooked or raw milk, anaphylaxis results through the inges-

tion of raw or cooked milk. As Besredka has already shown in non-alimentary anaphylaxis, the boiling of the milk does not destroy the sensitizing proteins.

The clinical facts make the researches in regard to anaphylaxis to mother's milk or to goat's milk in animals which are sensitive to cow's milk particularly interesting. In seven guinea pigs nourished with cow's milk and tested with mother's milk, three showed no anaphylaxis at all, three had a slight anaphylaxis, and one a very marked anaphylaxis. With goat's milk the anaphylaxis has been more frequent and definitely stronger. In six tested guinea pigs, two did not present any symptoms, one had a slight anaphylaxis, and three a very marked anaphylaxis. Thus, in guinea pigs sensitive to cow's milk, one can determine anaphylactic shock by testing them with mother's milk or goat's milk, and in our experiments, anaphylaxis has not been strictly specific for a specific variety of milk.

Recently, Kleinschmidt has contributed a very important study on alimentary anaphy-

laxis to milk. He has been easily able to sensitize some guinea pigs by ingestion, testing them afterwards by intracardiac injection. He has found that if, instead of boiling the milk for a few minutes, the boiling is prolonged for a quarter of an hour, the guinea pigs who drink the milk thus modified are sensitive in a varying degree. He has failed to prevent anaphylactic shock by ingestion. He has determined, morever, that this last ingestion does not protect the sensitive animals against a large injection by the intracardiac route, given two days after, which contradicted the results of Besredka already cited in regard to antianaphylaxis produced by the ingestion method.

Kleinschmidt has further studied the separate action of casein and other proteins. Anaphylaxis to lactalbumin is the most frequent. It may be associated with anaphylaxis to casein. However, casein does not produce sensitization to lactalbumin.

At the same time that we reported our experiments on milk anaphylaxis, a remark-

able article by Wells and Osborne appeared in which they studied alimentary anaphylaxis to vegetable proteins (Indian corn and barley) and described anaphylaxis to milk, eggs, and horse serum. Soon afterwards at the Congress of Paris, we reported definite proofs of alimentary anaphylaxis to eggs. By feeding some guinea pigs for many days a food to which was added one to two eggs per animal, we were able to produce, by a second intraperitoneal injection of the white of eggs, definite phenomena of anaphylaxis—shock, convulsions, etc. These reactions terminated with death in many cases. By repeating these experiments we definitely determined certain conditions necessary for the most successful production of experimental anaphylaxis to eggs. To us these seem comparable to clinical observations.

One of the most important requirements is to have the animals eat eggs in large quantities. If a quarter of an egg a day is given, anaphylaxis is slight or absent. On the contrary, the ingestion of an egg or more per day nearly always produces anaphylaxis.

We have, moreover, determined a fact of special interest; a small number of meals containing egg sensitizes the guinea pig; a large number immunizes him. If the animals are fed for a brief period (from one to three days) and if they are tested fifteen to twenty days after, the results are as follows:

A_4, death; A_3, very strong anaphylaxis; A_2, less anaphylaxis; A_1, slight anaphylaxis; A_0, no anaphylaxis at all.

Degree of anaphylaxis	A_4	A_3	A_2	A_1	A_0
Number of guinea pigs	7	1	3	2	3

Thus the ingestion of eggs during one, two, or three days, produces anaphylaxis nearly constantly (78 positive results in 100, not counting the instances of slight anaphylaxis A_1).

But if the guinea pigs are fed for from 14 to 16 days rather than for 3 days, anaphylaxis is less frequent. The following chart sums up our results:

Degree of anaphylaxis	A_4	A_1	A_0
Number of guinea pigs	2	1	5

Thus if the instances of slight anaphylaxis are not counted, positive results were obtained in 25 per cent of the animals.

If the feeding is prolonged for from 30 to 45 days, the percentage diminishes further and the following results are obtained:

Degree of anaphylaxis	A_3	A_2	A_1	A_0
Number of cases	2	1	1	19

Positive cases resulted in 13 per cent of the animals. The following chart sums up our experiments.

Number of days of feeding with eggs	3	17	45
Percentage of positive results	78%	25%	13%

In summary, the ingestion of eggs produces anaphylaxis when given for a few days, and immunity when given for a prolonged period. It is therefore a question of immunity, not of antianaphylaxis. If, in fact, eggs were taken away for 17 or 22 days from guinea pigs thus immunized by the ingestion of eggs for 45 days, the intraperitoneal injection produces insignificant or negative results. But according to Besredka, a lapse

of time from 7 to 21 days is sufficient to cause the anti-anaphylactic condition to disappear.[1]

Thus, from our experiments, we found that anaphylaxis was the first stage of immunity. Wells and Osborne had already arrived at the same conclusion in their researches in alimentary anaphylaxis to vegetable proteins. With vegetable proteins, it is even easier to obtain immunity than anaphylaxis. Wells and Osborne observed such immunity, and in addition a slight immunity to certain animal proteins. By feeding the guinea pigs with cow's milk, beef blood, and ovalbumen, they have actually been able to sensitize some guinea pigs. At the end of a month sensitization was greater than at the end of two months, indicating that immunity was beginning to be established.

Although alimentary anaphylaxis has been produced experimentally with certain common foods, such as meat, milk, eggs, vege-

[1] However, Besredka recently reviewed this problem and has decided that under our experimental conditions, anti-anaphylaxis can be prolonged.

table albumens, it has not resulted from all of them; for example, we have failed with mussels and Lesné with strawberries. Nevertheless, it is important to state that anaphylaxis has not been obtained under ordinary conditions of clinical alimentary anaphylaxis, for, though the animals were sensitized through the digestive tract, the anaphylactic shock was nearly always precipitated by an injection either subcutaneous, intraperitoneal, or intravenous.

In fact, if the requirements which Richet proposed to the International Congress of London in 1913 are accepted, alimentary anaphylaxis may be classified in the following groups:

Type A. A. (Alimentary, alimentary), which indicates sensitization by ingestion and shock by ingestion.

Type A. I. (Alimentary, injection), which indicates sensitization by ingestion and shock by ingestion.

Type I. A. Sensitization by injection and shock by ingestion.

Type A. A. is the one which occurs most often clinically. Type A. I. is that which is produced experimentally. It is sometimes observed in man; for example, in a case of Chauffard, a young girl who had eaten some raw horse meat and some hemostyl developed some intense symptoms following a subcutaneous injection of horse serum. It is very difficult to reproduce type A. A. experimentally. However, Richet has accomplished it in his experiments with crepitine. The ingestion of crepitine by dogs who had eaten it three weeks previously resulted in vomiting. This is what Richet has called the protective vomiting of anaphylaxis. As a result of it, animals can themselves get rid of the anaphylactic poison.

We have tried by many methods to produce such acute alimentary anaphylaxis, but have not succeeded, and Kleinschmidt has likewise failed.

The recognition of chronic alimentary anaphylaxis was of great interest. Nobécourt has already shown in a series of very

interesting experiments that the mortality of rabbits fed with ovalbumen was greatly increased, especially in young animals, and that it increased if the interval between the initial ingestion and the final ingestion was lengthened.

We have obtained some very suggestive though uncertain results in our guinea pigs which were fed for a long time with milk. Our guinea pigs frequently have been unable to tolerate satisfactorily the milk that we have fed them. In one of our experimental series (January, 1911), among 36 animals, 8 died very suddenly, whereas in the neighboring cages animals who ate ordinary food did not show an abnormal mortality. Moreover, besides the deaths in this series, the average weight of the animals was definitely lowered. In other series of experiments we have not observed the same phenomena. Certainly, consideration of our experimental results as well as the clinical observations do not point conclusively to the diagnosis of anaphylaxis, or, rather, chronic alimentary hypersensi-

tization; but such an interpretation does not seem illogical to us, in spite of its being uncertain.

In summary, most of the essentials of human alimentary anaphylaxis have been reproduced experimentally. However, our interest in experimental anaphylaxis depends, to a degree, less on the reproduction of the reactions observed clinically than on the explanation of them. Experimentation shows that the organism can be sensitized by ingestion and that this ingestion, under certain conditions, is comparable to a subcutaneous injection.

CHAPTER V

PATHOGENESIS

The pathogenesis[1] of alimentary anaphylaxis is evidenced at the present time by clinical observations and by certain experiments. The different conclusions arrived at by these two methods have shown that it is identical with the pathogenesis of anaphylaxis by the parenteral method. The subject can be sensitized through the digestive tract, if under very definite conditions; the ingested proteins are reabsorbed with little or no change and pass into the circulation as if

[1] The pathogenesis has been slightly modified. It seems to be clear now in 1929 although there are some points which are still obscure. Normally, food which penetrates into an organism has undergone such a transformation that it does not contain any protein—molecules which are not broken down into amino acids. In food anaphylaxis such transformation is not complete. The proteins, insufficiently modified, enter the blood stream and, as the organism is already sensitized, provoke pathological effects. One can understand why dyspeptic subjects are more easily sensitized than normal people.

they had been introduced there by the subcutaneous or intravenous injection.

The passage into the blood stream of ingested hetero-proteins is definitely reported in many articles. It is advisable to study successively those experiments which have been made on animals and those which concern man.

1. *Experimental researches* have been carried out on five different phases of the problem, which are indicated below:

(*a*) The presence in the serum of agglutinins, immune bodies, hemolysins, which appear to combine with the proteins.

(*b*) The presence of precipitins in the serum.

(*c*) The presence of protein itself with the aid of a specific precipitating anti-serum (Uhlenhut's method).

(*d*) The presence of foreign proteins in the urine.

(*e*) Modifications of the leucocytic count.

(*a*) In regard to agglutinins, Widal and Sicard have found specific agglutinins in the blood of young mice nourished by an animal whose serum agglutinated the d'Eberth bacillus. Ehrlich studied some mice immunized against abrin and ricin, who transmitted such immunity to their nursing offspring. Römer likewise found that tetanus and diphtheria antitoxins may pass through the milk of the mother to the young. Federici and R. Onoroto stated that, in the guinea pig, ingested antidiphtheritic serum entered the circulation, though in very small quantities.

We can next consider the studies of Maragliano, who reported an increase in antitubercular properties in the serum of rabbits and of dogs who had been fed his antitubercular serum, and those of Metchnikoff, who fed the blood of a horse to rabbits and rats and demonstrated specific hemolysins in their serum.

(*b*) The research studies on precipitins by Ascoli alone and with Bonfanti have yielded some positive findings. The serum

of rabbits nourished for a long time with ovalbumen contained abundant precipitins. On the contrary and under the same conditions, the precipitins were rare or absent in the dog. These results have been confirmed by Uhlenhut, Michaelis and Oppenheimer, Börnstein, Cantacuzène.

(*c*) The researches on heterogeneous proteins with the help of a specific precipitating antiserum have given fewer results. We will mention the positive experiments of d'Ascoli and Vigano, of Römer, of Pfeiffer, and of Schkarin.

(*d*) In animals, some foreign proteins in the urine have been discovered after the assimilation of white of egg, milk, beef juice, and serum (Ascoli and Vigano, Castaigne and Chiray, Linossier and Lemoine).

(*e*) Finally,[2] it is necessary to compare the experiments of Richet and Lassablière.

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[2] This pathogenesis is elucidated by a very interesting experiment of Arloing and Langeron, who gave a rather large amount of bile one hour before the sensitizing meal. The mucus which protects the intestinal cells is partly dissolved by this bile and the foods are then absorbed

Studying digestive leucocytosis in the dog, resulting from the ingestion of raw and cooked meat, they discovered that the first is considerably greater than the second and con-

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without being transformed as they should have been. They penetrate in this state into the portal veins. But if the liver is normal, these half-transformed substances are stopped.

We can here quote an old experiment of Claude Bernard. This author injected ovalbumen into the portal vein. No albumen passed in the urine. Then he injected the same quantity of ovalbumen into the vein of the ear of another rabbit, and he found that albumen passed into the urine. Thus the liver was shown to be a barrier against heterogeneous albumen. This remains true if the liver is normal, but this barrier may be broken down. In such a condition anaphylaxis may appear. We have always observed lesions of the liver in our animals sensitized to food. In sensitized nurslings, Barbier and Cléret also found identical lesions.

The adults who have food anaphylaxis generally present indications of an insufficiency of the liver. Indeed, many patients have extensive lesions of the liver such as cancer or cirrhosis, without any anaphylactic symptoms from food. Perhaps the organic deterioration in these patients modifies the humoral state in such a way that anaphylaxis can no longer develop. But if insufficiency of the gastric and intestinal secretions and insufficiency of the liver are necessary, are those two conditions sufficient for the production of food anaphylaxis? We don't think so, or rather we think that anaphylaxis is more frequent and more severe in patients whose vagosympathetic equilibrium and internal

clude: "Since the digestive process is practically the same for raw and cooked meats it follows that it is not digestion itself which

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secretions are disturbed. Indeed, we may notice that about all the manifestations of acute anaphylaxis depend upon the activity of the vagus and sympathetic nerves; the dyspnea or edema of the lungs, the muscle spasm of the bronchial tract, the paralytic vaso-dilation, etc. Atropin which paralyzes the vagus nerve and eserine which excites the sympathetic produce a diminution of the anaphylactic reaction. But we know that on each patient the vagosympathetic tonus is under the influence of internal secretions, especially of the thyroid gland. Generally, ablation of the thyroid diminishes anaphylactic manifestations in animals. The ingestion of large doses of thyroid increases the shock from peptone. Excitation of the vagus above the origin of the thyroid nerves acts in the same manner, although, below their origin, it does not modify it (Garrelson and Sautenoise). All these facts show that the symptoms of anaphylaxis are in part under the influence of the internal secretions and vagosympathetic tonus.

We can summarize our conception of the pathogenesis of food anaphylaxis as follows:

Food anaphylaxis is an intoxication. Substances not sufficiently modified (insufficiency of the digestive juice) pass through the intestinal barrier and the liver does not stop them sufficiently (insufficiency of the liver). They provoke an intoxication of the organism, especially of the blood (with hemoclassis) and they modify the internal secretions and vagosympathetic tonus. The symptoms are the more marked the greater the vagosympathetic instability.

produces digestive leucocytosis, but the presence of heterogeneous proteins."

2. With men these different methods have yielded varying results, according to the authors and ages of the patients who were studied.

(*a*) The transmission of tetanus and diphtheritic antitoxins through mother's milk to the infant has been observed by Salge and Much, Hamburger, etc.

(*b*) The precipitin method gives negative results with adults (Ascoli, Bornstein) but positive results with nurslings (More, Bauer, Hecker, Kleinschmidt, Feer).

(*c*) The researches made with the help of antiserum are likewise negative in the adult (Hamburger and Sperk, Keutzler), but positive in the nurslings (Ganghofner and Langer). L. Bernard, Debré, and Porak have reconsidered the problem and have shown that, after the ingestion of raw meat, some heterogeneous proteins pass into the general circulation of the blood of the adult in most instances but this passage is very rapid (15

to 20 minutes after eating) and is of short duration (results nearly always negative at the end of two hours).

(*d*) If digestive albuminuria is frequent, it has been difficult to demonstrate. It is only exceptional to find a foreign albumen in the urine (Chiray).

(*e*) Finally, Moro has found that there generally is a leucopenia during digestion in the breast-fed infants while the bottle-fed infant presents, under the same conditions, more or less marked leucocytosis, quite considerable in the child just weaned, which later nearly disappears. This entrance of proteins into the blood is frequent—even in the physiological state (Richet, L. Bernard).

Three conditions seem to facilitate this resorption of unaltered proteins in every case:

1. An excessive alimentation.

2. Insufficiency of digestive juices.

3. Spontaneous or induced lesions of the intestine.

1. *Excessive alimentation.*[3] — Previously Uhlenhut, Michaelis, and Oppenheimer found that it was necessary to have animals ingest considerable quantities of ovalbumen or of bovine serum in order to produce corresponding precipitins in their serum. Likewise, in our experiments on alimentary anaphylaxis to eggs, we have obtained positive results most frequently when large amounts of food were given in the experiments. With a quarter of an egg a day, we very seldom obtained any anaphylaxis; with two eggs a day, our results were frequently positive. The guinea pigs of Rosenau and Anderson sensitized to serum were only sensitized by means of ingestion of considerable amounts of raw meat.

[3] We think that the stomach pain or vomiting or the diarrhea which occurs a few seconds or minutes after ingestion of the sensitizing food are localized anaphylactic symptoms which may be compared to the Arthus phenomenon. A friend who suffered from gastric distress every time he took even one single drop of vinegar was tested by one of us with dilute vinegar by the cutaneous method. A positive reaction occurred. Although we were not successful in reproducing Arthus's phenomenon in gastro-intestinal tissue, we think that the gastro-intestinal phenomena are of this nature.

It is necessary then to ingest large amounts of a protein in order to obtain alimentary anaphylaxis experimentally. This has been corroborated frequently in clinical cases, as shown by the fact that most infants sensitized to eggs are those who have eaten one or two eggs a day in addition to their regular feedings.

2. *Insufficiency of digestive juices.*—Lesné and Dreyfus in one series of experiments remarkably executed and especially productive of theoretical and practical results have shown that the digestive juices play an important rôle and that they prevent the occurrence of anaphylaxis. By the injection of a small quantity of ovalbumen into the stomach or small intestine, they were unable to show that the animal was sensitized; by rectal injection, they obtained the opposite result. These last results are comparable to those of Léon Bernard, Debré, and Porak, who have demonstrated the passage into the blood of horse serum which had been injected into the rectum.

As a result of similar studies, Carnot and Slavu have shown that hydrochloric acid (.3 per cent) considerably diminishes the anaphylaxis to certain particularly fragile proteins, notably to serum. But as Lesné and Dreyfus have found, this reaction does not occur with more resistant proteins—such as actino-congestine in the dog, and ovalbumen in the rabbit. In other experiments, Lesné and Dreyfus digested ovalbumen with pepsin or pancreatin and showed that the digestive products were no longer anaphylactizing. They thus demonstrated the rôle of the digestive juices in sensitization through the digestive tract. They proved further that the action of the liver and that of the intestinal barrier were useful. However, the processes of digestion are not sufficient to destroy the anaphylactizing power of certain proteins, and in particular of toxalbumens. Other authors have tried to determine which of the products of protein digestion possess the power of sensitization.

One of the first problems was whether the products of peptic and tryptic digestion could sensitize the organism. Pick and Yamanouchi had obtained positive results, but the products that they fed, as Kleinschmidt remarked, still contained coagulable albumens and albumoses. On the other hand, Doerr felt very doubtful about the anaphylactic power of pure peptone. Zunz, experimenting with the four albumoses, separated by Pick from the products of the first stages of peptic digestion, has shown that three of them were of the "préparante" type and only two of them were of the "déchainante" type. Abderhalden and Weichardt have obtained only negative results with absolutely pure amino-acids. By an inverse process, Abderhalden and Kaempf have tried to determine if the injection of synthetic rather than more complicated forms of polypeptids can produce anaphylaxis. They have failed, although they used a very complicated polypeptid, such as l-leucyl-triglycyl-l-leucyl-octaglycl-l-leucine. Finally it is necessary for us to

mention the works of V. de Waele, who recognized a fundamental rôle of the amino-acids in the pathogenesis of anaphylaxis.

3. *Existence of spontaneous or induced lesions of the intestine.*—The presence of heterogeneous albumens in the serum has most often been discovered in infants afflicted with digestive disturbances (Lust, Moro). Experimentally the ingestion of small amounts of protein suffices to give positive results if the digestive mucosa has been previously injured with croton oil, tricresol, etc.

4. *Existence of hepatic lesions.*—Although experimentally it has not been possible up to the present time to demonstrate the rôle of the liver in anaphylaxis, the pathological studies prove that such a rôle exists. M.M. Barbier and Cléret, in an article as yet unpublished, have shown that certain infants sensitized to cow's milk presented severe hepatic lesions, periportal sclerosis and marked fatty degeneration. These infants were, moreover, usually afflicted with hereditary syphilis or hereditary tuberculosis, and

these authors suggest that the severe hepatic lesions that they observed probably were originally alimentary disturbances occurring during life. It is interesting to note that our guinea pigs sensitized to beef or milk also presented some very definite hepatic lesions.

Perhaps a certain degree of hepatic insufficiency explains the influence of pregnancy on alimentary anaphylaxis. This influence was very marked in a personal case and in the observation of Brazis already quoted. It may be that anaphylaxis occurs most frequently in children who eat too much and whose digestive juices are unadapted to proper digestion or who have digestive disturbances.

Further, there is a special permeability of the intestine to heterogeneous proteins in the infant, and especially in the newborn (Römer, Ganghofner and Langer, Uffenheimer, Keutzler, Moro, and Bauer).

The most serious anaphylactic reactions have been observed especially in infants. The question naturally arises whether hereditary

alimentary anaphylaxis is not due to an hereditary insufficiency of the digestive juices in regard to specific albumens.

It seems to us, in summary, that the three conditions that we have indicated are the most important in the production of alimentary anaphylaxis, both in the laboratory and in the clinic. But one objection perhaps can be made to such pathogenesis of alimentary anaphylaxis. If these conditions are sufficient to produce anaphylactic conditions, all individuals would become sensitized.

But alimentary anaphylaxis is rather exceptional and uncommon. It seems to us that the experiments of Wells and Osborne, as well as our own, allow us in a certain measure to appreciate the manner in which they originate. If animals are fed for a few days with a hetero protein they are anaphylactized. If they are fed for some weeks they are immunized. These experiments show that, after the anaphylactic state is produced, the daily ingestion of the foods results in a state of immunity.

Of these two antagonistic reactions, that of immunity is the stronger in the great majority of cases. It is only in the cases where the anaphylactic reaction overcomes the immunity that sensitization results. It is for this reason that they are rare. As Richet has reported to the Congress of London, it is through the continued and prolonged ingestion of proteins each day that immunization is established.

In summary, alimentary anaphylaxis develops into a general state of sensitization through the parenteral route, since some foreign substances penetrate into man's humoral fluids in various ways.

But the main problem of anaphylaxis remains, since its mechanism is still unsolved. Among the many theories of anaphylaxis which have been proposed, it is possible to recognize three principal types.

1. *Theory of Richet.*—Richet believes that the injection of an antigen results in the formation in the organism of a substance which is non-toxic by itself, called toxogenin.

A further injection of the same antigen brings about different reactions, owing to the combination of antigen (toxin) with this toxogenin, as expressed in the following equation:

Toxogenin (performed in the organism of the prepared animal) plus Antigen (Toxin)

equals Apotoxin (Anaphylatoxin of Friedberger)

Toxogenin and antigen are in themselves non-toxic, but apotoxin formed by the union of these two atoxic bodies is toxic. This reaction can be compared to the following reaction:

Amygdaline (non-toxic) plus emulsine (non-toxic)

equals Hydrocyanic Acid (Toxic)

This theory is substantiated in the experiments of passive anaphylaxis and active anaphylaxis. Richet has mixed the blood of a sensitized animal with the antigen and has injected the mixture into a young animal with fatal results, whereas neither the serum

nor the antigen was toxic in the same doses. Moreover, passive anaphylaxis produced with serum (experiments of Nicolle and Richet) entirely corroborates this theory. This is the chemical theory of anaphylaxis.

2. *Theory of precipitins of Friedberger.*— This is the biological theory of precipitins, proposed originally by Marfan (1905).

It depends on a very interesting experiment of Friedberger. He mixed antigen and serum. A precipitin was formed, collected, and redissolved. This precipitin was toxic. Many objections can be raised to this theory. The main one is the following: Certain very sensitive subjects have no precipitins, while other subjects whose blood is very rich in precipitins show no symptoms of anaphylaxis.

3. *Physical theories.* — These are the theories of Besredka, Wassermann, Keysser and Bordet, of Widal, Abrami, Brissaud, and Joltrain. A physical interpretation of anaphylactic reactions was originally formulated, we believe, by Besredka. The phenomena of anaphylaxis and of anti-anaphylaxis are re-

duced to the reactions of precipitation and absorption which govern the amount of colloids present.

This theory depends on a certain number of experiments which had for their object the demonstration that anaphylactic shock could be brought about by a series of intoxications of which that of peptone is the best known. Friedberger, with a mixture of typhoid bacilli, horse serum, and fresh guinea pig serum, H. Keysser and Wassermann with a mixture of kaolin and fresh guinea pig serum, Bordet with a mixture of gelatin and unheated guinea pig serum, Widal and his pupils with human serum or even a solution of NaCl or of bicarbonate of soda, have presented many examples of it.

Bordet thinks that the anaphylactic poison comes from the serum itself. It originates there but becomes united with an antagonistic substance. A certain number of substances, such as those which produce aphylactic or anaphylactoid reactions, are active in destroying this complex substance and in ab-

sorbing the antagonistic material. Since symptomatology is identical, whatever antigen is used, it is found that the poisoning is eventually of the same type, being due to the products of humoral dissociation.

Widal, Abrami, Brissaud, and Joltrain, in some investigations of the greatest interest, have formulated a theory of anaphylaxis likewise founded on the physical modification of blood equilibrium. Through different procedures (first injection of albuminoid substances in large doses, injection of sodium chloride, or of bicarbonate of soda), they have been able to produce reactions whose symptoms are identical with those of anaphylaxis.

The clinical reactions are well known—chills, fever, vomiting, diarrhea. The blood changes are characterized by what has been called "the hemoclastic crises," which have been specially studied in alimentary anaphylaxis. This hemoclastic crisis is characterized by three main features: hypotension, leucopenia, and retarded coaguability of the

blood. This crisis can exist alone, in the absence of other clinical symptoms. This is an extremely interesting theory and has the advantage of explaining by a single mechanism certain reactions of analogous symptomatology and of different etiology.

Of these theories, which is correct? This is impossible to decide definitely at the present time. The chemical theory is based on the experiments of anaphylaxis *in vitro,* and of passive anaphylaxis. The physical theories depend on the conclusions of Friedberger, Wassermann and Keysser, of Bordet and Widal.

Perhaps these different theories are not irreconcilable, and one may say that apotoxin formed chemically by the combination of toxogenin and toxin acts by producing some modifications of the complex colloids of the serum, which modifications might likewise be produced by other substances.

But there remains the most characteristic feature of anaphylaxis which is sensitization —that is to say, reactions which rapidly

appear after the second injection of weaker doses.

It is best, we believe, not to adopt different pathogeneses for anaphylaxis and for immunity. Anaphylaxis and immunity are undoubtedly related in a definite but rather obscure manner. Anaphylaxis often obscures immunity (Richet). It constitutes, perhaps, the first stage of it (Richet and ourselves). On the other hand, the humoral states of skeptophylaxis and anti-anaphylaxis appear very closely related, and both seem to be special types of immunity. It seems to us, especially from the study of alimentary anaphylaxis, that very little difference exists between anti-anaphylaxis and immunity. Perhaps it is a question of theory rather than of fact. The practical importance of the conclusions of Besredka, however, is not diminished.

CHAPTER VI

DIAGNOSIS

Since the clinical manifestations of alimentary anaphylaxis are quite varied, none of them being pathognomonic, the diagnosis is often difficult.

I. Positive Diagnosis

The diagnosis of alimentary anaphylaxis depends less on symptoms than on etiological factors. In order to determine that anaphylaxis is the cause of observed acute reactions, it is necessary to recognize the following facts:

(*a*) The sensitizing food may not produce any reaction, or only some slight ones (by direct toxic action) on the first ingestion.

(*b*) The reactions occur with each new attempt made to accustom the subject to the food to which he is sensitized, provided that the ingested amount be small.

(*c*) The reactions appear suddenly, immediately after subsequent ingestion.

In severe anaphylaxis the various symptoms, identical with those of experimental anaphylaxis, constitute as a whole a typical enough picture to be of real diagnostic value; shock, convulsions, dyspnea, hypotension, urticaria, diarrhea, vomiting. But in mild anaphylaxis, the symptoms are often isolated (urticaria, repeated prurigo, eczema, migraine, etc.) and are not in any way characteristic. The diagnosis must depend entirely on etiological circumstances whose value we have indicated.

The data from which the diagnosis of mild or chronic anaphylaxis is established are comparable but less precise.

1. The food is well tolerated when it is first eaten. It is only ultimately and progressively that reactions occur.

2. These reactions gradually disappear when the food contact is removed and they reappear but slowly when the food is eaten again.

3. The observed reactions are chiefly digestive, cutaneous (chronic eczema, urticaria), repeated migraine, respiratory spasm, and asthma.

4. These manifestations of chronic anaphylaxis may be interspersed with periods when acute reactions are predominant.

Laboratory methods.[1]—Two procedures have been employed in order to demonstrate

[1] The cutaneous or the intradermal test has been developed since 1914 into a most important diagnostic procedure. It is a classical method in the United States, and too many contributions have been published by various specialists in that country to necessitate a description of it at this place. Food tests, however, can be negative in very definite instances where food allergy is present. We will describe the symptoms which may result from the cutaneous test, and which, I think, have been reported by one of us for the first time. A man had a sensitization to haricot beans. We made a cutaneous test with the bean extract. The test was negative, but in the night the patient was awakened by diarrhea with mucus identical to that which the eating of the beans usually produced.

The other method, which is less frequently utilized, is the method of passive anaphylaxis, which was first proved experimentally. We were not able to reproduce it, but Sales and Verdier and Drago were more fortunate. They injected into the abdomen of guinea pigs from two to five cc of blood from a food-sensitive patient, and, twenty-four

the anaphylactic nature of observed reactions —one, direct: passive anaphylaxis; the other, indirect: method of precipitins.

The first method consists in injecting into an animal the blood of the subject supposed to be in a state of anaphylactic sensitization. Within two days the animal is tested with the sensitizing substance. In certain cases of medicinal anaphylaxis (antipyrin, quinine, iodoform, serum) positive results have been obtained with this test (Bruck, Manoiloff, Grysez and Bernard, Achard and Flandin). However such results have not always occurred (Pagniez). In cases of alimentary anaphylaxis, this method has been used very rarely.

Bruck especially has had two positive results in two cases of anaphylaxis to pork. In a case of anaphylaxis to cow's milk (Feer) and in a case of alimentary anaphylaxis to mussels (Flandin and Tzanck) positive re-

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hours after, they tested them with an intracranial injection of the same food. The animals in general died from eight to ten hours afterward.

sults have occurred; on the contrary, one of us has failed in a case of recurrent urticaria resulting from the ingestion of rayfish. The rarity of these positive results obtained in alimentary anaphylaxis does not surprise us. Experimentally we have nearly always failed in alimentary anaphylaxis to milk and always in anaphylaxis to eggs.

The indirect procedure has only rarely been used. Finizio has twice reported the presence of precipitins in the blood of a child sensitized to milk. One child who eventually lost his sensitization no longer showed any precipitins. This method should be used in other cases in the future.

II. Differential Diagnosis

It is often difficult to diagnose alimentary anaphylaxis, where the history from the etiologic viewpoint is not clear, since the observed symptoms are not all characteristic —except perhaps in their association—and since the biological methods are still undeveloped.

Where the gastro-intestinal symptoms dominate the picture, one should first think of serious affections of the abdomen: peritonitis, appendicitis, obstruction, or intestinal perforation, hepatic colic, renal or lead colic.

Certain types of indigestion, especially in children, indicate serious digestive disorders. If they repeatedly follow overeating the diagnosis may be easy. If they are due to common foods the case is often puzzling, though the reactions are apt to be less acute. They are displayed by all those who have eaten the poisonous food. In fact, such a conclusion can be quite definite, since those foods which frequently produce alimentary poisoning are known: pastry cream and St. Honoré cake in particular, sausages, gelatin, game pie, preserved meat, especially veal. Sometimes the crustacea or the mollusks and certain fish from the Antilles and the China Sea can be incriminated. In mushroom poisoning the diagnosis is founded on the history and progressive development of the symptoms.

Certain types of enteritis are characterized by very definite symptoms. In very acute enteritis of later infancy (dry cholera), the clinical picture is nearly identical with that of anaphylaxis. However, the beginning is less abrupt and there is no cutaneous manifestation.

The acute adrenal insufficiency can reproduce the complete picture of anaphylaxis; hypotension, asthenia, diarrhea, and vomiting. But the histories are different. This is nearly always secondary to an infectious malady (scarlatina, erysipelas, typhoid fever).

When the anaphylactic attacks are repeated, one may suspect a spasm of the pylorus in the infant and of cyclic vomiting in older children.

According to certain authors, particularly Halberstadt and Lesné, the pyloric spasm can be due to alimentary anaphylaxis to milk, at least in certain cases, especially when with it is associated hypertrophy of the pylorus.

Finally, when a careful analysis of the facts has shown that the observed reactions

are due to the ingestion of a definite food, it becomes necessary to try to differentiate anaphylaxis from the intolerance that certain subjects have for certain foods. This decision is often impossible. In fact, the symptoms are identical. Barnathan in his thesis reports two observations of Guinon as cases of anaphylaxis which really are cases of simple intolerance. The repetition of the same reactions occurred with each ingestion of the same food.

The history alone should make it possible to decide the question. Anaphylaxis[2] only occurs when the first ingestion has produced only slight, if any, symptoms. However, with the exception perhaps of anaphylaxis to cow's milk in nurslings, it is exceptional to have patients under observation from the beginning of a food sensitization. The patients only remember an intolerance to the specific food in youth. With Gelpke's patients, the

[2] It is known today that food sensitization frequently arises *in utero* or through the mother's *milk* (Walzer, Balyeat, Shannon, O'Keefe).

anaphylaxis or intolerance was hereditary. With Landmann's patient, the symptoms occurred after eating the first egg and increased progressively. Thus, one would hardly know whether or not these phenomena of idiosyncrasy should be classed as anaphylactic manifestations.

CHAPTER VII

TREATMENT

The treatment must be based on etiology.

1. The preventive treatment is the most important. Since overfeeding may result in sensitization, it is important to carefully avoid all alimentary excess. This rule should be applied especially to newborn or undernourished children, dystrophics, those afflicted with gastro-enteritis, or premature infants. It should likewise be applied to children from one to five years of age who very often become sensitized to eggs. Such children should not be given more than one egg a day. In fact, eggs should be kept away during convalescence from gastro-enteritis.

2. The treatment of mild anaphylactic reactions is standardized. The temporary withdrawal of the sensitizing food from the diet should be complete, at least at the start. This will generally be sufficient. The resumption

of the normal diet will demand the same precaution as in the case of acute anaphylaxis.

3. Acute reactions necessitate active therapeutic measures. The treatment is that of nervous shock—injections of camphorated oil, ether, adrenalin. It is necessary to put the patients at the same time on a liquid diet. Lesné and Dreyfus in fact have shown experimentally that sensitized animals do not present any anaphylactic manifestations if they are fed before the initial injection.

4. After the anaphylactic crisis, it is agreed that the gastro-intestinal reaction and blood of the infant become modified. The treatment must be directed toward the inherited tendency. It will be sufficient to study this for milk and eggs.

If the child is sensitized to cow's milk, this should be replaced by mother's milk. There is an absolute indication for this and it is necessary to abstain from repeated trials with cow's milk. Such repetition resulted in death in the case of Finkelstein. If it is impossible to procure a nurse for the child, ass's

milk (Hutinel and Barbier) or goat's milk should be tried. However, the specificity of anaphylaxis is not absolute either clinically or experimentally. At the same time the digestive function of the intestinal tract may be improved by the use of pepsin and pancreatin.

If the infant is old enough or if feeding with mother's milk or ass's milk is impossible, it is important to place it exclusively on a purely carbohydrate diet.

Can one resume the use of cow's milk after it has been discontinued for a time? We have seen the danger of repeated trials; death has been observed in three cases (Finkelstein, Finizio, Halberstadt). Some authors have had good results in using cow's milk again—for example, Halberstadt, in three cases. However, he agrees that it is necessary to be extremely cautious in all cases.

Schlossmann has proposed a method based on immunization by the subcutaneous injection of minimal and increasing doses of beef

serum. "It is possible," he says, "to determine whether or not a child has already received cow's milk for nourishment by the reactions resulting from the injection of 0.1 cc of bovine serum. From the intensity of the resulting reaction in an infant previously nourished entirely on the breast, it can be decided whether he possesses a slight or marked tendency to react to cow's milk, a tendency which might result in definite difficulties at weaning, because of the persistence of such idiosyncrasy. It is possible, by an increasing injection of the serum (0.1 gram) to protect the children afflicted with idiosyncrasies to cow's milk and in whom this food has the effect of a poison."

We have not verified the researches of Schlossmann, but his conclusions appear quite likely to us, since in some unpublished experiments we have obtained comparable results. Certain guinea pigs injected with mother's milk became sensitive to a second injection of human serum. Many of them died from anaphylactic shock. Nevertheless,

his method is used at times and we desire to recommend it.

Finizio, inspired by the work of Besredka on the immunizing effect of small doses of milk, has had good results in giving it to his patients. The milk has been ingested only where it was known, from previous determination, that a small dose was well tolerated. It is best to eliminate milk for a definite time —two or three months—so that the digestive tube will be entirely normal. One may then try to desensitize the patient to cow's milk by giving very small doses. By using this method the desensitized or immunized organisms may possibly be able to tolerate milk in increasing quantities. Finkelstein proposes a beginning dose of two or three drops a day, increasing this gradually to several cubic centimeters. By this method large amounts at times may be taken. One of us has used this very satisfactory method successfully on a baby who had an anaphylactic intolerance to cow's milk. The milk was given in a pap in which it was cooked. It

is advisable, with such children, to continue giving milk in the form of pap and to give up whole milk for a long time.

Let us consider the problem of alimentary anaphylaxis to eggs. The therapy is comparable to that of milk. Schoffield's patient was immunized by giving him homeopathic doses of eggs (1 to 10,000) which were progressively increased.

Lesné immunized his little patient by first giving some well cooked eggs, mixed with flour in the form of dry cakes, later soufflèd, then in the form of the cooked egg itself in very small quantities.

Recently, P. Pagniez and Pasteur-Vallery-Radot, J. Héranet and Fr. Saint-Girons have successfully used a quicker method than that of the use of small doses progressively increased. The patient of P. Pagniez and Pasteur-Vallery-Radot, intolerant to all the ingested proteins, was protected without difficulty against any reaction and could eat all foods with impunity by taking a cachet of 0.5 gram of peptone one hour before meals.

The patient of J. Héran and Fr. Saint-Girons was a malarial case with an intense anaphylaxis to quinine. He could tolerate perfectly increasing doses of this medicine, by eating a cachet containing 5 milligrams of quinine and 0.5 gram of bicarbonate of soda an hour before meals. These results of desensitization therapy through the intestinal tract should be kept in mind because of the frequency of symptoms due to alimentary anaphylaxis and various medicinal intolerances.[1]

[1] The following ideas in regard to therapy are offered in our review of 1929. The ingestion of a "small meal" containing all kinds of food, which are to be taken one hour later at the regular meal, helps as a desensitizing measure in some cases. Peptone therapy is certainly more practical. One hour before meals one and one-half grams of peptone are administered. Now the peptones which are used are generally mixed peptones; they come from meat, eggs, milk, and fish and are mixed before use. On the contrary, the intradermal injection of peptone (50 per cent) or the repeated skin reactions (Vallery-Radot) seldom give good results. We don't think that the injections of milk under the skin of nurslings sensitized to this food should be used. Weil of Lyons has had good results with this method, but it may result in serious reactions. In some forms of chronic anaphylaxis, very good results are obtained by autohemo-

therapy, which seems to us, because of its lack of danger, preferable to isohematotherapy (and especially to auto or isoserotherapy). Autohemotherapy is begun with an injection of 5 cc and increased in a progressive way up to 15 or 20 cc. With serotherapy, the beginning dose must be 0.01 cc intravenously and one must use it with great care; the dose must not be increased over 2 or 3 cc. We do not recommend it. The injection of blood may be made every two days for about eight or ten doses. We do not know the mechanism of this therapy but it may be associated with protein shock.

The pathogenic treatment must always be used. It is the most rational but it is not easy to apply. We must work against the gastro-intestinal and hepatic insufficiency and against the hypervagotonus which is so frequent in sensitized subjects. It must be remembered that in such patients, fasting, or the lactovegetarian diet, or heliotherapy, or the subcutaneous injections of mineral water, may give good results and modify the anaphylactic state.

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